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THE EFFECT OF VITAMIN K_1 OXIDE ON HYPOPROTHROMBINEMIA INDUCED BY DICOUMAROL*

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BOSTON

MUCH attention has recently been given to the use of dicoumarol as an anticoagulant. The advantages of the drug over heparin, such as oral activity and relatively low cost, are apparent, but the serious disadvantage of lack of control has been given less attention.[1] Overman et al.[2] point out that in rats vitamin K has an action antagonistic to that of dicoumarol. Shapiro et al.[3] gave small doses of dicoumarol to patients and found that the combined oral and parenteral administration of large amounts of 2-methyl-1, 4-naphthoquinone — a synthetic compound similar to vitamin K — prevented the prolongation of the prothrombin time following the administration of dicoumarol.

It seemed advisable to determine whether vitamin K has any influence on the action of dicoumarol given in therapeutic doses. It was evident that very large doses of the vitamin would be required because usual doses, or even those ordinarily thought to be large, have been shown repeatedly to be ineffective.[4-7] An occasional report concerning the control of large doses of dicoumarol by vitamin K has appeared in the literature.[8]

Fieser[9] and Seligman et al.[10] have pointed out that the synthetic compound 2-methyl-1, 4-naphthoquinone differs greatly, both chemically and physiologically, from true vitamin K_1 or K_2. Furthermore, it is known that this compound has produced toxic effects in small animals.[11] Therefore it seemed inadvisable to administer large doses to patients.

True vitamin K_1 oxide,§ synthesized by the method of Fieser[12] and prepared for use as suggested by Davis et al.[13] was employed in this investigation. The amount of vitamin K_1 oxide was accurately measured either volumetrically or by weighing. The latter method is probably more accurate. From 100 to 450 mg. of vitamin K_1 oxide in oil form was dissolved in 15 to 20 cc. of absolute alcohol. The resulting solution was poured slowly, with sterile precautions and constant agitation, beneath the surface of 1000 to 1500 cc. of 5 or 10 per cent glucose in water. A fine suspension of the vitamin was thus obtained. The patients received by intravenous administration 1000 to 1500 cc. of this preparation. The time of administration varied from three to five hours. No serious untoward effects were noted. Two patients complained of headache and 1 vomited following the injection. The amount of alcohol administered produced no untoward effect except the production of a mild euphoria in some patients.

The dicoumarol‖ was used in the form of the crystalline compound and administered orally in gelatin capsules.

The prothrombin times were determined by a modification[14] of the method of Quick.[15]

RESULTS

The effect of the administration of vitamin K_1 oxide on the hypoprothrombinemia produced by dicoumarol was studied in 5 patients. Two methods of attack were used. In one an attempt was made to prevent dicoumarol from having its customary hypoprothrombinemic effect. In the other the full effect of dicoumarol was permitted to occur and vitamin K_1 oxide was then administered in an attempt to bring the prothrombin concentration back to normal.

Figure 1 demonstrates the preventive action of 180 mg. of vitamin K_1 oxide on the effect of di-

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§The vitamin K_1 oxide was kindly supplied by Dr. Arnold Seligman, of the Beth Israel Hospital, Boston, and by Merck and Company, Rahway, New Jersey.

‖The dicoumarol was kindly supplied by the Abbott Laboratories, North Chicago, Illinois.

coumarol administered orally in a dose of 500 mg. Following the administration of the dicoumarol, the patient's prothrombin time rose from a normal value of twenty-eight seconds to a maximum of fifty seconds two days after the administration of the drug. Twelve days later a second dose of 500 mg. of dicoumarol was administered. Five hours later the intravenous injection of vitamin K_1 oxide was commenced and 180 mg. was administered in the next two hours. As shown in the figure there was no significant change in the prothrombin time of this patient when the vitamin K_1 oxide and dicoumarol were administered in the doses and under the conditions described above. After a lapse of twelve days, a third dose of 500 mg. of dicoumarol was administered without the simultaneous administration of vitamin K_1 oxide.

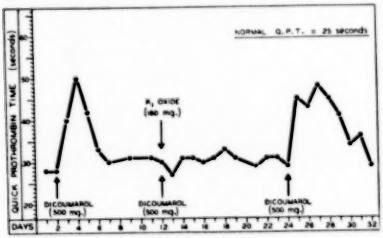

FIGURE 1. *The Preventive Action of Vitamin K_1 Oxide on the Hypoprothrombinemia Induced by Dicoumarol.*

The response to the dicoumarol was prompt and the usual hypoprothrombinemia resulted. It should be noted that following the first administration of dicoumarol five days elapsed before the prothrombin level returned to normal, and following the third administration a period of eight days was required to obtain this result.

Figure 2 demonstrates the effect of the administration of vitamin K_1 oxide on the hypoprothrombinemia obtained following the administration of dicoumarol. In this patient 500 mg. of dicoumarol was insufficient to produce a marked hypoprothrombinemia, and a second dose of 1 gm. of the drug was therefore administered three days later. The prothrombin time rose from a normal value of 25 seconds to 55 seconds in a period of two days. At that time, 250 mg. of vitamin K_1 oxide was administered intravenously. A prompt reduction in the prothrombin time occurred. In four hours it fell to 35 seconds, and in twelve hours to 31 seconds, and in twenty-four hours it returned to its original normal value. Four days after the prothrombin time was normal, a second dose of 1 gm. of dicoumarol was administered, with a consequent rise in prothrombin time from 25 seconds to 75 seconds over a period of two and a half days. However, six and a half days elapsed before the prothrombin time returned to normal, in sharp contrast to the rapid reversal of the hypoprothrombinemia observed when vitamin K_1 oxide was administered. This important difference in rate of return is demonstrated more

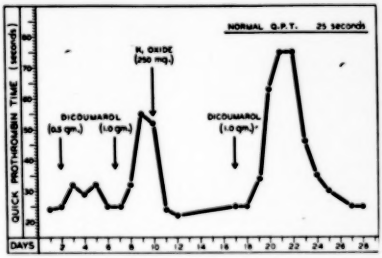

FIGURE 2. *The Antagonistic Action of Vitamin K_1 Oxide on Dicoumarol.*

clearly in Figure 3, in which the fall of the prolonged prothrombin time produced by dicoumarol, with and without the administration of vitamin K_1 oxide, is plotted in hours.

Three other patients were studied with respect to the action of vitamin K_1 oxide after the hypoprothrombinemia from dicoumarol had been established. The dose of dicoumarol used varied from 500 mg. to 1 gm. In 2 patients vitamin K_1 oxide was administered in a dosage of 350 and 450 mg., respectively, in two doses. In one of these

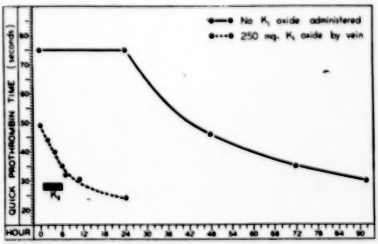

FIGURE 3. *The Effect of Vitamin K_1 Oxide on the Hypoprothrombinemia Induced by Dicoumarol.*
This is a portion of the curve shown in Figure 2, with the readings plotted in hours instead of days.

patients the prothrombin concentration returned to normal in fourteen hours, and in the other in twenty-four hours. The third patient was given

200 mg. of vitamin K_1 oxide after the hypoprothrombinemia had been established, without significant effect. Unfortunately, it was impossible to make further studies on this patient, but probably the dose administered was too small.

Discussion

In 4 of 5 patients studied, the administration of vitamin K_1 oxide in large doses either prevented or reversed the hypoprothrombinemia produced by suitable doses of dicoumarol. Just as with the anticoagulant effect of dicoumarol, the amount of vitamin K_1 oxide required to produce an antagonistic effect varies from patient to patient and repeated doses of the vitamin may be necessary to secure the desired result. The quantitative relation between dicoumarol and vitamin K_1 oxide requires further study. Furthermore, it should be noted that the effect of vitamin K_1 oxide presented in this paper is confined exclusively to its effect on the hypoprothrombinemia produced by a *single* dose of dicoumarol. It will be necessary, therefore, to establish the usefulness of the vitamin as a means of controlling the coagulation time in patients who are receiving a prolonged course of dicoumarol. If, under these circumstances, it can be established that vitamin K_1 oxide acts in a similar fashion to that obtaining for a single dose of dicoumarol, it would seem likely that many of the dangers following the use of this anticoagulant can be removed.

Summary and Conclusions

The activity of large doses of vitamin K_1 oxide in reversing the hypoprothrombinemia produced by dicoumarol has been demonstrated in 3 out of 4 patients studied. It is probable that an inadequate amount of the vitamin was administered to the fourth patient.

In 1 patient, the administration of vitamin K_1 oxide prevented the subsequent establishment of a hypoprothrombinemia following the administration of dicoumarol.

The amount of vitamin K_1 oxide required to produce the desired effect varied considerably from patient to patient.

No serious toxic manifestations were observed from the administration of large amounts of vitamin K_1 oxide. The only untoward action observed in this small series of patients was transient headache and, in 1 patient, vomiting.

It is suggested that the action of vitamin K_1 oxide in reversing the hypoprothrombinemia established by single doses of dicoumarol may make the therapeutic use of this anticoagulant safer than it has heretofore been.

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CARDIAC ARRHYTHMIAS FOLLOWING PNEUMONECTOMY*

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AURICULAR flutter and auricular fibrillation may occur as functional disturbances in cases in which no definite evidence of heart disease is present.[1-14] Ritchie[2] and others[3, 4] as early as 1914 observed that flutter sometimes occurred when there was no evidence of heart disease. Parkinson and Bedford[5] reviewed 52 cases of flutter and discovered 5 patients who had no detectable heart disease. Orgain, Wolff and White,[1] in reviewing 5000 cardiac consultation cases, found that 36 (6 per cent) of 583 cases of fibrillation and 5 (14 per cent) of 38 cases of flutter occurred when no detectable heart disease was present. This indicates the rarity of these two conditions, especially functional auricular flutter. The purpose of this paper is to emphasize the relative frequency of cardiac arrhythmias, especially functional auricular fibrillation and flutter, following pulmonary resection.

In a series of 78 patients on whom total pneumonectomy was performed at the New England Deaconess Hospital, 4 cases of auricular fibrillation, 2 cases of auricular flutter, 1 case of flutter-fibrillation and 1 case of nodal tachycardia were encountered postoperatively. An additional case of auricular fibrillation was observed following a right middle and lower lobectomy. The right lung was removed in 3 cases, and the left lung in 6 cases. The patients' ages varied from thirty-two to sixty-six years. There were 6 males and 3 females. No history of rheumatic fever or syphilis was elicited. All patients except one (Case 4) had negative blood Hinton tests. One had a slight elevation of the systolic blood pressure (160 mm.), which later dropped to normal.

X-ray films taken at six feet revealed cardiothoracic ratios well below 50 per cent in all cases. Five patients had normal preoperative electrocardiograms. Careful history-taking and physical examination failed to reveal evidence of heart disease in any case before operation.

The arrhythmias appeared on the second, third (2 cases), fifth, seventh, fourteenth and fifteenth days following pneumonectomy. In Case 6, flutter followed left pneumonectomy by twenty-nine days and pericardiostomy for a sterile pericarditis by only one day. In Case 9, fibrillation followed pneumonectomy by fifty-seven days and thoracoplasty by ten days. That the procedures mentioned precipitated the arrhythmia in Cases 6 and 9 is probable. In 8 cases normal sinus rhythm was restored within forty-eight hours by rapid digitalization. In Case 7 there were two transient attacks of auricular fibrillation; one ceased spontaneously, and the other thirty minutes after a test dose of 3 gr. of quinidine sulfate. The duration of the arrhythmias in 7 cases was between thirty and forty-eight hours. The remaining 2 cases, both of fibrillation, lasted two and ten hours, respectively.

A follow-up of these 9 cases in December, 1942, varying from eight months to five years after the arrhythmia, revealed that no patient had developed cardiac decompensation or had had a return of the cardiac arrhythmia.

Case Reports

Case 1. T. K., a 45-year-old housewife, was admitted on December 29, 1936, complaining of chronic cough for 4 years and occasional blood-streaked sputum for 2 years. In 1934 she had a paroxysm of tachycardia of 2 hours' duration. In November, 1936, bronchoscopy and biopsy showed carcinoma in the left main-stem bronchus. Pneumothorax was given.

Physical examination was negative except for left pneumothorax and slight clubbing of the fingers. The usual laboratory findings were negative except for a white-cell count of 22,950. X-ray study showed a left pneumothorax with atelectasis of the left upper lobe. The cardiothoracic ratio was less than 50 per cent. An electrocardiogram was normal except for a tachycardia of 108.

On January 5, 1937, a one-stage left pneumonectomy was done. The course was satisfactory until the 19th postoperative day, when the pulse suddenly rose to 172. It was regular and not changed by carotid or ocular pressure. The patient was conscious of the tachycardia but was not distressed. An electrocardiogram showed a nodal tachycardia with a ventricular rate of 170. Eighteen grains of digitalis was given in the first 24 hours, the first 3 gr. intramuscularly and the rest by mouth. Thereafter 1½ gr. was given daily until February 5, when the digitalis was discontinued. The pulse remained rapid and regular for 48 hours, when it returned to a normal rhythm at 110. An electrocardiogram showed a normal sinus rhythm with a rate of 116.

When examined 4 years after the operation, she stated that she had been free from symptoms except for a moderate pulmonary hemorrhage 1 year previously.

Case 2. S. S., a 43-year-old Syrian saleswoman, was first seen on March 14, 1938, complaining of intermittent hemoptysis for 1 year and an almost continuous vague discomfort in the left lower anterior chest for 11 months. The latter was not related to exercise or excitement.

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The only abnormality in the physical examination was diminished breath sound in the left axilla. Routine laboratory tests were negative. X-ray study showed atelectasis in the lower part of the left upper lobe. The cardiothoracic ratio was less than 50 per cent. A bronchiogram showed obstruction of the lingular branch of the left upper lobe bronchus. Preoperative pneumothorax was then begun.

On April 11, a left total pneumonectomy was performed, two 500-cc. blood transfusions being given. The pathological report was adenocarcinoma of the left upper lobe. The patient did well until the 7th postoperative day, when she developed a sudden tachycardia of 170. She perspired and the skin felt clammy, but there were no other symptoms. An electrocardiogram showed auricular fibrillation, with a ventricular rate of 150. Twelve grains of digitalis was given in the first 12 hours and 1½ gr. a day thereafter for 10 days. Thirty-six hours after the onset of tachycardia the pulse returned to normal.

The patient has been symptom free since then.

Case 3. S. K., a 55-year-old Russian merchant, was first seen on November 24, 1940, complaining of pain in the right chest and down the right arm for 5½ months. The physical examination and laboratory examinations were negative except for signs suggestive of atelectasis of the right upper lobe and moderate wasting of the small muscles of the right hand. X-ray examination showed a normal cardiac shadow with a cardiothoracic ratio of 39 per cent and atelectasis of the right upper lobe. Bronchoscopy revealed a mass protruding from the right upper lobe bronchus, subsequently proved to be carcinoma.

On December 13, after a preparatory right pneumothorax, exploratory thoracotomy was performed, which showed mediastinal metastases. Palliative pneumonectomy was done, three 500-cc. blood transfusions being given. Except for a transient atelectasis of the left upper lobe that necessitated bronchoscopic aspiration on the 3rd day, the course was satisfactory until the 5th postoperative day, when the pulse suddenly rose to 170. Although the patient had no complaints, slight sweating was noticed. An electrocardiogram showed auricular flutter-fibrillation. Twenty-four grains of digitalis was given in the first 24 hours, and 1½ gr. daily thereafter. After 20 hours the pulse dropped to 84 but again became rapid after ½ hour. Normal rhythm returned permanently 48 hours after onset. An electrocardiogram was normal except for slightly lowered amplitude of the QRS complexes. One week later, an electrocardiogram showed wide, slurred QRS complexes with depressed ST segments in all leads. The PR interval was 0.13 second. The digitalis was discontinued, and subsequently the ST segments and QRS waves returned to normal. The patient was discharged symptom free 42 days after operation.

Three months later an electrocardiogram was normal. Death from metastatic carcinoma occurred 11 months after discharge.

Case 4. C. Y., a 66-year-old, Chinese banker, was admitted on January 11, 1941, complaining of cough for 5 years and occasional hemoptysis for 2 years.

Physical examination was negative except for dullness and diminished breath sounds anteriorly and posteriorly over the lower half of the right lung and a few crepitant rales at the right base. The usual laboratory findings were negative except that the blood Hinton test was repeatedly positive. The electrocardiogram was essentially normal. X-ray examination showed a shadow suggestive of atelectasis of the right upper lobe. The cardiac shadow was of normal size and the cardiothoracic ratio was 43 per cent. Bronchoscopy and biopsy showed epidermoid carcinoma in the right lower lobe bronchus.

Following pneumothorax, an exploratory thoracotomy revealed that the mediastinum was invaded by the growth. A palliative right middle and lower lobectomy was performed, during which two 500-cc. blood transfusions were given. On the 2nd postoperative day the pulse suddenly rose to 190 and became irregular. The electrocardiogram showed auricular fibrillation. Fifteen grains of digitalis was given in the first 12 hours, 16½ gr. in the first 24 hours, and 1½ gr. daily thereafter. Normal cardiac rhythm returned after 48 hours. There were no further cardiac symptoms.

The patient died of metastatic carcinoma 6 months after operation.

Case 5. N. W., a 55-year-old retired manufacturer, was admitted on January 23, 1941, complaining of a slight cough for 1½ years and occasional vomiting for 1 year. He had lost 45 pounds. He took large quantities of alcohol.

Physical examination was negative except for a blood pressure of 160/88, a few crackling rales in the left midchest posteriorly and transient moist rales at the right base. The usual laboratory tests were negative except for a red-cell count of 3,540,000, many red cells in the urine and a urinary albumin was 0.1 per cent. A diagnosis of idiopathic hematuria was made after thorough study, including intravenous and retrograde pyelograms. An electrocardiogram was within normal limits except for evidence of slight right-axis deviation. X-ray study showed a normal cardiac shadow, with a cardiothoracic ratio of 40 per cent and an infiltration in the region of the left hilum suggesting neoplasm.

On February 3, after a preliminary left pneumothorax, a one-stage left pneumonectomy was carried out, three 500-cc. blood transfusions being given. The left vagus nerve was found imbedded in the tumor mass and was resected. Convalescence was satisfactory until the 3rd postoperative day, when the pulse suddenly rose to 165 and became irregular. An electrocardiogram showed auricular fibrillation. Twenty-four grains of digitalis was given in the first 24 hours, and 1½ gr. daily thereafter. Normal rhythm, confirmed by electrocardiogram, returned after 48 hours.

The patient was well when examined in January, 1942. An electrocardiogram at that time was normal except for evidence of slight left-axis deviation.

Case 6. R. R., a 34-year-old clerk, entered the hospital January 28, 1941, complaining of an intermittent cough for 6 years. In 1937, bronchoscopy and biopsy had shown a benign adenoma in the left main-stem bronchus. Deep x-ray treatments and intrabronchial radon were given. The cough and sputum decreased but slight occasional hemoptysis continued. There had been dyspnea on exertion for several years, but no edema, orthopnea or palpitation had been present.

Physical examination was negative except that the left chest was limited in motion and there were dullness, harsh breath sounds and many rales over the lower half of the left lung field. The usual laboratory findings were negative. The Decholin circulation times from arm to tongue were 15.0 and 14.4 seconds. Ether circulation

times from arm to lung were 7.8 and 6.0 seconds. The venous pressure was 86 mm. of water. The vital capacity was 2380 cc. A preoperative electrocardiogram was normal. X-ray study showed atelectasis of the left lower lobe and a large emphysematous cyst of the left upper lobe. The mediastinum was deviated to the left. The exact cardiac thoracic ratio could not be obtained owing to marked displacement, but the heart appeared to be of normal size. Bronchoscopy and bronchography showed marked saccular bronchiectasis of the entire left lung.

On February 11, a left pneumonectomy, with four 500-cc. blood transfusions, was carried out. The course was satisfactory until the 19th postoperative day, when the patient developed a sharp substernal pain not related to respiration. The temperature rose to 102°F. every afternoon and a moderately loud pericardial friction rub appeared. For the next 9 days the patient became progressively worse. The liver increased in size and became tender. An electrocardiogram showed low QRS complexes and low T waves. The venous pressure rose to 200 mm. of saline solution on the 27th postoperative day. A diagnosis of pericarditis with effusion was made, and on March 11, the 28th postoperative day, the pericardium was explored and found to be approximately 0.5 cm. in thickness and shaggy. A loculated collection of approximately 100 cc. of clear fluid was found. The culture was sterile. The following evening the pulse was 170 but regular. An electrocardiogram showed auricular flutter. Twenty-four grains of digitalis was given in the first 24 hours and 1½ gr. daily thereafter. Normal rhythm, confirmed by electrocardiogram, returned in 30 hours. The liver size returned to normal, the abdominal discomfort disappeared, and there was no more chest pain. Improvement was steady. The patient was discharged on August 22.

There had been no more cardiac symptoms when the patient was examined 1 year later.

Case 7. J. B., a 49-year-old clerk, was admitted on June 15, 1941, complaining of cough and soreness of the right chest for 7 months and blood-streaked sputum for 5 months. A bronchoscopic examination and biopsy on May 23 had shown epidermoid carcinoma of the right main-stem bronchus.

Physical examination was negative except for slightly impaired resonance over the right apex above the level of the 3rd rib anteriorly. The usual laboratory tests were normal. The Decholin circulation time from left arm to tongue was 19 seconds. A preoperative electrocardiogram was normal with the exception of R_4, which was only 1 mm. high. The cardiothoracic ratio at x-ray examination was 44 per cent.

On June 19, following a preliminary pneumothorax, a one-stage right pneumonectomy, with three 500-cc. blood transfusions, was done. The course was satisfactory until the 3rd postoperative day, when a rapid, irregular pulse was first noticed. An electrocardiogram showed auricular fibrillation with a ventricular rate of 160. Less than 2 hours later normal rhythm spontaneously returned. An electrocardiogram was normal, R_4 being 4 mm. high. The pulse remained regular and between 84 and 98 until the 6th postoperative day, when the patient was awakened by a "fluttering" in the chest and the pulse rate was found to be rapid and irregular. He was given 3 gr. of quinidine sulfate as a test dose. Thirty minutes later the pulse had returned to a normal rhythm of 86.

When seen 3 months later the patient was free of cardiac symptoms.

Case 8. A. M., a 48-year-old man, was admitted on April 7, 1942, complaining of cough with occasional blood-streaked sputum of 1 year's duration, with a loss of 10 pounds in weight.

Physical examination was negative except for dullness with absent breath sounds over the left upper lung field. The usual laboratory findings were negative except for a red-cell count of 3,860,000 and a white-cell count of 19,900. X-ray study showed consolidation of the upper third of the left lung. The heart appeared normal. The cardiothoracic ratio was well below 50 per cent but could not be measured accurately. A diagnosis of pulmonary abscess was made.

On April 16, following preliminary left artificial pneumothorax, a total left pneumonectomy was performed, three blood transfusions being given. The left phrenic nerve was intentionally crushed. The course was satisfactory until the 15th postoperative day, when a regular pulse of 186 developed. The patient was unaware of the tachycardia. An electrocardiogram showed auricular flutter with a ventricular rate of 170 and an auricular rate of 340. Sixteen and a half grains of digitalis was given in 24 hours. The pulse at the end of that time was 166. During the next 14 hours he received 6 gr. of digitalis. The flutter lasted for 36 hours. On May 3 an electrocardiogram showed a regular sinus rhythm with a rate of 126. An electrocardiogram on May 5 showed sinus tachycardia, with a rate of 132, and one on May 21 showed sinus rhythm with a rate of 118.

There were no further cardiac symptoms.

Case 9. A. R., a 32-year-old woman, was admitted on April 6, 1942, with a 6-year history of pulmonary tuberculosis limited to the left lung. She had had extrasystoles for many years. On February 19, a left pneumonectomy had been done. The postoperative course was satisfactory and the patient was discharged on March 18. She was readmitted for thoracoplasty.

Physical examination was negative except for the lung findings. The usual laboratory examinations were negative. X-ray study showed a clear right lung but pneumohydrothorax on the left. The cardiothoracic ratio was well below 50 per cent but could not be measured accurately.

On April 8, a left thoracoplasty was performed. The course was satisfactory until the 10th postoperative day (8 weeks after the pneumonectomy), when the patient vomited three times without obvious cause and immediately afterward developed a rapid, irregular pulse of 160 to 170. An electrocardiogram showed auricular fibrillation. One and a half grains of digitalis was given intramuscularly, followed by 7½ gr. orally during the next 10 hours. At that time normal rhythm returned for 1 hour, followed by a return of the rapid and irregular rate for 10 minutes. Thereafter the normal rhythm was permanent. Two days later an electrocardiogram was normal.

Discussion

Attempts have been made to discover the cause or precipitating factors that initiate these arrhythmias. The fact that arrhythmia occurred in 8 of 78 cases following pneumonectomy, an incidence of nearly 10 per cent, whereas none occurred in 63 cases following single lobectomy, suggests that the more extensive procedure is essential

to its production. With total pneumonectomy there has been a decided shift in the mediastinum away from the affected side, and later in every case a pleural effusion has developed that required frequent thoracentesis. Although difficult to prove, this shift in the mediastinum may play a part in initiating these abnormal rhythms.

Following closure of the bronchus with silk mattress sutures after pneumonectomy, the vagus nerve on that side naturally falls in close apposition to the closed bronchus, if not actually in contact with it. Therefore infection of the bronchial stump or a stitch abscess in this area would be apt to irritate the vagus nerve. One indication of such an infection may be a rise in temperature. The case records were examined with this in view, and it was found that 2 cases showed a moderate rise in fever at the time the arrhythmia began. One of these patients had been afebrile for one week, when the fever rose to 101°F. without detectable cause. On the third day of fever the arrhythmia began. In 4 cases there was a slight but definite rise in temperature on the day of onset of the arrhythmia. Another patient had a continued temperature after operation, and on the seventh day of fever the tachycardia began. In 1 case the arrhythmia began the day after surgery, when fever is normally present, and hence could not be considered from this point of view. Only 1 patient remained afebrile at the time of the arrhythmia. If this hypothesis is correct, it would explain the variable latent period that follows the operation before onset of the arrhythmia, since the time of onset of the stitch abscess may vary. That vagal stimulation may induce fibrillation under certain conditions has been reported by several workers.[15-18]

One might consider further that the mediastinal shift acts like thyroxin or the faradic current and represents the E factor of Nahum and Hoff,[16] and that the E factor combines with vagal stimulation, as suggested by these workers, to induce the arrhythmias.

Sulfathiazole powder was introduced into the chest cavity in 5 cases and sulfanilamide powder in 2 cases. No sulfonamide drug was used in 2 cases. Five patients received sulfathiazole orally after operation, whereas 4 received none. All operations were done under intratracheal cyclopropane anesthesia. It seems unlikely that any of these drugs were related to the arrhythmia.

Summary and Conclusions

Functional cardiac arrhythmias, especially auricular fibrillation and auricular flutter, occurred in 8 of 78 patients who received total pneumonectomy but had no evidence of heart disease. In our opinion, these arrhythmias alone do not indicate heart disease.

It seems best to restore the heart to normal rhythm as soon as practicable, either by rapid digitalization or, in selected cases, by quinidine sulfate, since heart failure may result if an excessively rapid cardiac rate continues over many days.

The etiology of these arrhythmias is unknown. The hypothesis is suggested that the precipitating factor is vagal irritation from a stitch abscess or infection of the bronchial stump in the presence of hyperexcitability of the auricular muscle resulting from marked displacement of the mediastinum.

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CARDIAC ARRHYTHMIAS FOLLOWING THORACIC SURGERY*

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DISTURBANCES in the rate and rhythm of the heart action are occasionally observed in surgical patients during the postoperative period. The frequency of such occurrences is not high, and no pertinent statistics on this subject are to our knowledge available, although several observers[1, 2] have noted the frequency of arrhythmias during operation. The uncommonly high incidence of cardiac arrhythmias following thoracic surgery has come to our notice during the last two or three years and deserves some comment. Although at times this complication during the postoperative period is of small consequence and quickly rights itself, at other times it is prolonged and difficult to control. Under such circumstances the physician is confronted with a therapeutic problem that, if not corrected, may result in embarrassment of the heart and the circulation.

In the last few years 12 patients (9 of whom had electrocardiograms) presenting a disturbance in cardiac rhythm following thoracic surgery have been observed in the Massachusetts General Hospital. Nine of these were drawn from a series of 43 patients with carcinoma of the lung who underwent lobectomy or pneumonectomy, a proportion of 21 per cent. The remaining 3 cases were drawn from 13 cases in which exploration (3 cases) or resection (10 cases) of carcinoma of the esophagus was performed. A brief account of these 12 cases is given herewith.

CASE REPORTS

CASE 1. B. M., a 47-year-old Jewish salesman, entered the hospital with a history of productive cough for 7 months, which had been severer for 1 month. For 1 week he had had an intermittent fever as high as 103°F. Physical examination was not remarkable. X-ray examination of the chest revealed an area of increased density that was thought to be due to an abscess of the right lower lobe. On October 14, a right lower lobectomy was performed. Two days later, following the patient's turning on his side and coughing, the pulse became totally irregular at 150 and the lips became somewhat cyanotic. The patient was digitalized in the course of 24 hours, by which time the heart had returned to a normal rhythm. He did poorly, however, and died of infection on October 19, 5 days postoperatively. No autopsy was performed.

Comment. This case illustrates the somewhat transient arrhythmia that may be precipitated by a change of posture. The auricular fibrillation lasted for less than 24 hours.

CASE 2. F. H., a 65-year-old salesman, entered the hospital with the complaints of wheezing, hemoptysis and some shortness of breath for 8 months. Physical examination revealed a few musical rales throughout the chest. The heart was normal. The blood pressure was 130/80. An x-ray film of the chest demonstrated a mass in the left upper lobe that was thought to be a bronchiogenic carcinoma. On October 25, a left pneumonectomy was performed. The blood pressure dropped postoperatively but returned to normal after 1 liter of air under positive pressure was removed from the left chest. Two days later, the pulse was found to be irregular because of frequent auricular premature beats by electrocardiogram, at a rate of 120. The patient was digitalized, since at first the arrhythmia was thought to have been due to auricular fibrillation. Five days postoperatively, auricular flutter was observed with an auricular rate of 360 and a ventricular rate of 180 with 2:1 block (Fig. 1). The dosage of digitalis was increased, and the following day the ventricular rate was 120 and there were varying degrees of block. Three days later, a normal rhythm at 100 to 120 with auricular premature beats was observed. The following day auricular flutter was again noted, with a ventricular rate of 160 (2:1 block), and the digitalis dosage was again increased. Two days later, the rhythm was regular at a rate of 120. Later the same day the patient became increasingly dyspneic and cyanotic and died of respiratory distress with the pulse remaining at about 120.

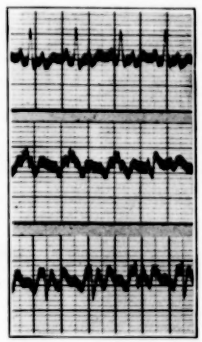

FIGURE 1. *Case 2.*

The electrocardiogram shows auricular flutter with 2:1 auriculoventricular block.

Autopsy revealed the following conditions: epidermoid carcinoma of the left lung (previous operation) with metastases to the liver, kidney and right lung; acute postoperative pleuritis, on the left; acute fibrinous pericarditis; bronchopneumonia; and pulmonary edema and emphysema, on the right.

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Comment. In spite of the intermittent arrhythmia, there were few signs of heart failure until the last few hours of life. The use of digitalis may have accounted, in part at least, for the lack of more evidence of congestive heart failure. In reviewing the case, however, it appears that quinidine might have been used to great advantage to prevent or control the cardiac arrhythmia. The frequent auricular premature beats in the first electrocardiogram were a sign of an irritable heart.

CASE 3. R. B., a 41-year-old laborer, entered the hospital complaining of chest pain and wheezing of 6 weeks' duration. Physical examination revealed a moderate number of musical rales throughout the chest, with some impairment of breath sounds over the right chest anteriorly. The heart was normal. The blood pressure was 100/60. An x-ray film of the chest revealed a mass at the right lung root that seemed to occlude partially the bronchus to the right upper lobe. On May 2, a right pneumonectomy was performed. The patient did well except for the development of moderate subcutaneous emphysema. On May 13, a tube was inserted in the right thorax for drainage of fluid from an empyema. On May 20, the pulse was found to be totally irregular with an apical rate of 135 and a radial pulse of 90. This, however, was readily converted to a normal rhythm in 3 or 4 minutes when the intrathoracic pressure was changed from negative to positive (−5 cm. of water to +2 cm.). No recurrence of the arrhythmia was noted, and the patient recovered from the operation.

Comment. The cardiac arrhythmia was of small moment, in this case, but it demonstrates a factor that may influence the cardiac rhythm, that is, a change in intrathoracic pressure on one side of the chest. Change in the position of the heart may have resulted from the change of pressure.

CASE 4. K. B., a 57-year-old physician, entered the hospital for observation because of a mass found incidentally by x-ray in the right lung field. The chest and heart were normal. The blood pressure was 110/70. On April 14, a right upper lobectomy was performed for carcinoma of the lung. The postoperative course was uneventful, although the patient was kept in an oxygen tent. On April 14, after he had been out of the tent for a short while, the pulse reached 160, with some irregularity but without deficit. An electrocardiogram revealed the presence of auricular flutter. The patient was digitalized, and the following day the heart rate had decreased to an average of 90, with varying degrees of heart block, from 2:1 to 5:1. Digitalis was continued and the heart rate was fairly well controlled, in spite of the persistence of the auricular flutter, although at times the rate rose to 120. The patient had a slow convalescence with some cyanosis, mental confusion at times and a high carbon-dioxide blood level, which was apparently due to a poor gaseous exchange in the lungs. In July, quinidine sulfate, 0.4 gm. every two hours for six doses, was given in an attempt to restore normal rhythm, but without success. Auricular flutter persisted without acting as a factor of clinical moment until death from cerebral metastatic malignancy occurred the following November.

Comment. This case illustrates the long and protracted auricular flutter that may follow thoracic surgery. Digitalis was of aid in controlling the ventricular rate.

CASE 5. H. L., a 55-year-old merchant, entered the hospital complaining of cough and hemoptysis of 5 months' duration. The heart was normal and the blood pressure was 140/70. X-ray examination of the chest revealed a mass in the right upper lung field, thought to be carcinoma. The electrocardiogram revealed a normal tracing except for an inverted T wave in Lead 4, which was interpreted as being consistent with mild coronary heart disease. Because of a slightly painful right calf with mild swelling of the leg on entry, the right superficial femoral vein was ligated on February 13. On February 24, a right upper lobectomy was performed. Auricular fibrillation was noted February 28 (Fig. 2), at which time some fluid was noted in the right chest and the trachea was deviated to the right. Quinidine sulfate was given, 0.4 gm. the first day and 0.8 gm. the 2nd day, at which time the rhythm returned to normal. Following this for 4 weeks 0.2 gm. of quinidine was given three times a day as a prophylactic measure. On March 5, the patient was suddenly seized with a painful constricting sensation across the chest, with increase in the respiration to 35 and in the pulse to 140, with regular rhythm. On the following day, the electrocardiogram (Fig. 3) was quite characteristic of pulmonary embolism with acute cor pulmonale. The same day, tenderness was noted in the left calf, and ligation of the left superficial femoral vein was performed, with removal of a thrombus from the vein. The patient subsequently improved rapidly without further complications.

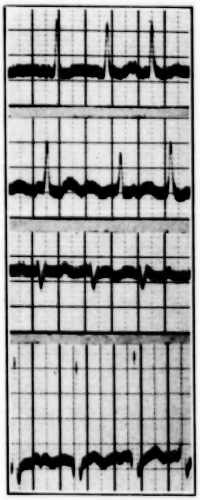

FIGURE 2. *Case 5.*

This electrocardiogram, taken four days postoperatively, demonstrates auricular fibrillation with a ventricular rate of about 145.

Comment. It seems likely that quinidine aided in the restoration of normal rhythm. This case also illustrates the occurrence of constricting chest pain quite typical of angina pectoris following a large pulmonary embolism, probably due to decreased coronary blood flow. This is more likely to occur in a patient who has some antecedent coronary heart disease, as was suggested in this case by the slightly abnormal electrocardiogram. It is also of interest that the patient did not develop auricular fibrillation following pulmonary embolism. The maintenance dose of quinidine may have been of some value in this regard.

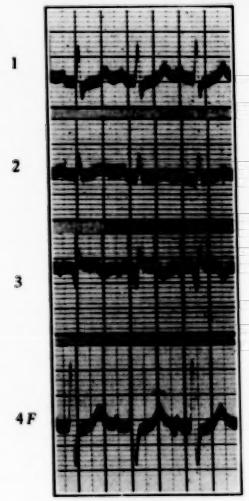

FIGURE 3. *Case 5.*

This electrocardiogram was taken nine days postoperatively but less than twenty-four hours following pulmonary embolism.

CASE 6. E. R., a 56-year-old truck driver, entered the hospital because of morning cough and loss of weight for 6 months. The heart was normal. The blood pressure was 130/70. X-ray examination of the chest revealed a mass in the left upper lung field that was thought to be due to carcinoma. On July 6, a total left pneumonectomy was performed. The course was uneventful until July 9, when auricular fibrillation was noted at a rate of 120. The patient was digitalized, and the heart rate was thereafter controlled. He developed fever on July 20, and died from infection on July 22.

Autopsy revealed the following conditions: epidermoid carcinoma of the left lung, with metastases to the regional lymph nodes and contralateral lung; bronchopleural fistula, on the left; septicemia, nonhemolytic streptococcus; and bronchopneumonia (right lower lobe).

CASE 7. J. G., a 57-year-old salesman, entered the hospital with a diagnosis of probable carcinoma of the left bronchus. Physical examination revealed diminished breath sounds over the left lower lobe. The remainder of the examination was not remarkable. The blood pressure was 120/80, and the pulse was regular. On May 22, a left pneumonectomy was performed. On May 24, auricular fibrillation was noted, with an apical rate of 110. The patient was given digitalis, 0.3 gm. daily for 7 days, at the end of which time the apical pulse had decreased to 85. Digitalis, 0.1 gm. daily, was continued until discharge. It is not known whether the rhythm was irregular at discharge, but the rate was 80.

Comment. The auricular fibrillation in this case was of little importance and presented no therapeutic problem during the postoperative course.

CASE 8. W. K., a 56-year-old plumber, was referred to the hospital with a diagnosis of carcinoma of the upper lobe of the right lung. Physical examination was not remarkable, and the blood pressure was 120/80. On May 5, a right total pneumonectomy was performed. Three days later, the heart rate was 160, and an electrocardiogram demonstrated auricular flutter at a rate of 320, with 2:1 auriculoventricular block. Eight tenths of a gram of digitalis was given in the subsequent 24 hours, at the end of which time a second electrocardiogram revealed a normal rhythm at 120 with frequent auricular premature beats. A brief recurrence of the rapid heart action shown to be auricular flutter with a ventricular rate of 160 was observed both on May 11 and May 12, each lasting about 1 hour. There were no more episodes of disturbed heart action, and the remainder of the course was uneventful. Digitalis was stopped on May 16.

Comment. Again, the transient nature of the tachycardia is demonstrated. It should be noted, however, that evidence of irritability of the heart was manifested at times, in the absence of auricular flutter, by the frequent auricular premature contractions.

CASE 9. J. McC., a 39-year-old mechanic, was referred to the hospital with a diagnosis of carcinoma of the lung. Physical examination was not remarkable, the heart was normal, and the blood pressure was 110/70. On May 26, a right pneumonectomy was performed. On May 31, auricular fibrillation was noted, with a ventricular rate of about 190, and this continued until June 2, when the heart rate was regular at 80 with an occasional extrasystole. Later the same day auricular fibrillation was again noted, with a ventricular rate of 195. The patient was digitalized, which resulted in a decrease of the ventricular rate to 130. The following day 700 cc. of fluid was removed from the right chest. By June 4, the heart rhythm was again normal at a rate of 80 and remained so throughout the postoperative period. Digitalis was continued until discharge.

Comment. The transient nature of the auricular fibrillation is again notable. The accumulation of fluid in the right chest developed about the same time as the auricular fibrillation.

CASE 10. C. H., a 61-year-old laborer, entered the hospital complaining of difficulty in swallowing of 3 weeks' duration. Physical examination was not remarkable. The blood pressure was 155/90. X-ray examination of the esophagus revealed an irregular filling defect in the mid-

dle third that was thought to be carcinoma. On July 15, a partial esophagectomy was performed through the left thorax. The postoperative course was uneventful until July 20, when the respirations increased to 30, the pulse rose to 135, and there were physical signs of collapse of the left lower lung. On July 22, the patient became mentally confused and the heart rate was found to be 180. He was digitalized, and the following day the heart rate was regular at 140. The signs of collapse of the left lower lung lobe had disappeared by July 25, at which time the pulse was regular at 95 and the mental confusion had disappeared. Convalescence was uneventful.

Comment. The postoperative period was first complicated by collapse of the left lower lobe, to be followed by the development of auricular flutter and a rapid ventricular rate. Digitalis probably helped to slow the rate, and after 3 days normal rhythm was re-established.

Case 11. C. W., a 53-year-old man, was admitted to the hospital because of epigastric pain of 5 weeks' duration. The heart and lungs were normal. The blood pressure was 140/70. X-ray examination of the esophagus revealed a tumor in the lower third. On August 3, partial esophagectomy was performed through a left thoracic approach. On August 5, auricular fibrillation was noted, with a ventricular rate of 180. The patient was digitalized and 3 days later the apical rate was 100, with normal rhythm. The digitalis was discontinued after 2 weeks, and the heart rhythm remained regular. Convalescence was uneventful.

Case 12. J. L., a 49-year-old housewife, entered the hospital because of dysphagia of 7 months' duration. Physical examination was not remarkable. The blood pressure was 130/80. X-ray examination of the esophagus revealed an ulcerative lesion in the lower third. On September 29, a transthoracic partial esophagectomy was performed. On October 3, auricular fibrillation developed, with a ventricular rate of 200. Quinidine sulfate was started, and 2.8 gm. was given in the first 24 hours. At the end of this time the rhythm returned to normal for 1 hour at a rate of 110, following which auricular fibrillation recurred with a somewhat slower ventricular rate of 140 to 160. The quinidine was continued, the patient receiving 2.8 gm. during the 2nd day, in 0.4-gm. doses. On October 6, the pulse returned to normal and it remained regular thereafter. The following day, 1500 cc. of fluid was removed from the left chest. Convalescence was uneventful.

Discussion

Of the 12 patients reported here, 8 developed auricular fibrillation and 4 developed auricular flutter. In 2 cases auricular premature beats were noted, either preceding or subsequent to the tachycardia. In no case was there noted a change from auricular flutter to auricular fibrillation or vice versa, but in 4 cases there was at least one recurrence of the arrhythmia following a restoration of normal rhythm. Thus quinidine therapy seems to be justified if auricular premature beats develop or even following the restoration of normal rhythm to prevent any further arrhythmia. It can also be used as a prophylactic measure, particularly in patients who undergo partial esophagectomy, since 3 of 10 patients in our experience developed cardiac arrhythmia. Quinidine sulfate, 0.2 gm. three or four times a day, has proved effective in this regard. This need not be given until after the operation, since the arrhythmia does not develop until from two to eighteen days postoperatively.

It is undoubtedly significant that all the patients reported here were thirty-nine years of age or over, the average being fifty-three and range from thirty-nine to sixty-five. In a considerably larger series of patients who underwent lobectomy or, less frequently, pneumonectomy for bronchiectasis of the lung, no cases of arrhythmia of the heart were observed. The ages in that series were much lower, ranging from about fifteen to forty years. Age, then, is a predisposing factor in the development of cardiac arrhythmias following thoracic surgery. This has been noted likewise in patients with otherwise normal hearts in whom a cardiac arrhythmia develops.[1-3]

In the series of 12 cases reported here, examination of the heart gave no evidence of valvular disease. In 1 patient (Case 5) there was some electrocardiographic evidence of coronary heart disease. However, it has been noted by several observers[1, 3-5] that there seems to be no significant association of auricular fibrillation and coronary heart disease. It seems likely, therefore, that coronary heart disease played no important role in the development of the cardiac arrhythmias in this series. It is true that all the patients had carcinoma, but this is undoubtedly irrelevant.

The cause of the development of the arrhythmias remains obscure, although there seemed to be precipitating factors in several cases. In 3 cases the development of empyema coincided with the onset of the arrhythmia of the heart, and in 1 there was significant collapse of the lung that developed concomitantly. The change of posture of 1 patient seemed to have initiated the cardiac arrhythmia. Pericarditis was found at necropsy in 1 case, but it seems unlikely that pericarditis was an important etiologic factor in this series.

In treating the patient who develops an arrhythmia, the physician has the choice of giving no special treatment, since most of these patients spontaneously re-establish normal rhythm in the course of two or three days, of attempting to control the ventricular rate by the use of digitalis and waiting for the normal rhythm to return or of attempting to hasten the restoration of normal rhythm by quinidine sulfate. The decision should be based on the condition of the patient, since immediate therapy may be necessary to allay congestive heart failure. Rapid digitalization is then indicated. If there is no imminent danger of

congestive heart failure, a course of quinidine sulfate, 0.4 gm. every two to three hours for six doses, or until normal rhythm is restored, is the treatment of choice. If this fails, the same course may be repeated, using 0.6 gm. every two to three hours under careful electrocardiographic control.

Summary and Conclusions

Cardiac arrhythmia is occasionally noted following thoracic surgery. Twelve patients are reported from a series of 56 who underwent surgery for carcinoma of the lung or esophagus. Eight had auricular fibrillation, and 4 auricular flutter.

Age appears to be a predisposing factor, since arrhythmia of the heart seldom occurs following thoracic surgery below the age of forty.

Quinidine sulfate may be used to advantage in such patients as a prophylactic measure during the postoperative period.

Since the above report was compiled, a thirty-year-old woman has been observed who developed nodal tachycardia at a rate of 180 fifteen hours after a left lower lobectomy for tuberculosis and bronchiectasis. A course of quinidine sulfate, 0.4 gm. every two hours for five doses, was given during the first day without effect on the tachycardia. The patient was also digitalized during this time by the administration of 1.6 mg. of lanatoside C intravenously. A second course of quinidine was given, consisting of 0.6 gm. every two hours, and after the fourth dose, thirty-six hours after the onset of the tachycardia, the rhythm returned to normal and the pulse dropped to 110. Quinidine sulfate, 0.4 gm., was continued every six hours in an effort to prevent the recurrence of the paroxysmal tachycardia. The patient developed increasing cyanosis and died of infection on the fourth postoperative day. The pulse rate remained between 110 and 120 until the time of death.

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MEDICAL PROGRESS

BRIGHT'S DISEASES*

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DESPITE considerable elaboration since the original description by Bright more than one hundred years ago, the group of nephropathies now embraced by the term "Bright's diseases" continues to pose many problems in etiology, pathologic physiology and therapy. In discussing this group of renal disorders, usually defined as the bilateral nonsuppurative nephropathies, a logical classification is desirable. The threefold classification of Volhard and Fahr[1] continues to be popular, either in its original form or in various modifications. Volhard and Fahr's division of Bright's diseases into the inflammatory nonsuppurative nephropathies (nephritides), the degenerative nephropathies (nephroses) and the vascular nephropathies (nephroscleroses) has had a new modification during the past year by Ellis[2-4] in England. He also proposes three groups of entities — nephritis, essential hypertension and a miscellaneous group. The present review will follow, in the main, the classification of Volhard and Fahr, but will be confined to a discussion of the nephritides and the nephroses. The omission of the nephroscleroses is dictated by the desire to avoid repetition, for this subject is usually discussed with essential hypertension and should be considered in relation to all aspects of hypertension.

The articles in the medical-progress series of 1941 have been published in book form (*Medical Progress Annual*, Volume III. 678 pp. Springfield, Illinois: Charles C Thomas, 1942. $5.00).

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The Nephritides

Glomerulonephritis

The pathogenesis of glomerulonephritis remains obscure. A considerable amount of work has incriminated the streptococcus as the commonest etiologic agent, although other infectious agents have been implicated as causative factors in isolated cases. There seems to be little doubt that upper respiratory infections, usually by beta-hemolytic streptococci, precede the attack of acute diffuse glomerulonephritis in the vast majority (90 per cent in one series[5]) of cases in this country. It is interesting to note the comment made by Snapper[6] that a superficial pyodermatitis is the usual form of infection preceding acute diffuse

glomerulonephritis in China. However, Seegal and Earle[7] found that approximately two thirds of their patients with glomerulonephritis had a "deep" infection. Additional evidence incriminating the streptococcus in most cases of nephritis is to be found in changes in the antistreptolysin titer during the disease, with an increased titer appearing in the acute stage.[8] During the past year it has also been found that the titer increases in the course of exacerbations of chronic diffuse glomerulonephritis and that the magnitude of the increase is correlated with the severity of the exacerbation and not with the severity of the preceding infection.[9, 10] The increase in antistreptolysin titer is often valuable in detecting a recent infection by Group A hemolytic streptococci, although the organisms may not be demonstrable by culture.

Just how the streptococcus damages the kidney is unknown, for there is no evidence that it directly invades the kidney or has a nephrotoxic effect. Attempts to produce nephritis in animals with streptococci and their products have been, on the whole, inconsistent and unsatisfactory. However, a type of glomerulonephritis closely resembling the human form has been produced in animals by the use of "nephrotoxic" serums and may throw light on the mechanism of damage by the streptococcus. So-called "nephrotoxic nephritis" may be produced in the guinea pig, dog, cat or rabbit by injecting serum from ducks or chickens previously subjected to sensitizing doses of kidney tissue from the same species in which the nephritis is to be induced.[11] On the surface, this nephritis appears to be caused by a simple reaction between antigen (the recipient animal's kidney) and antibody (the donor's serum). However, if this were the case, the reaction would be expected to occur immediately instead of after five to eight days, as actually found. Moreover, the development of nephritis seems to depend on the presence in the recipient's blood of antibodies reacting with the donor's serum. These antibodies are manufactured during the latent period, and their appearance in the blood marks the onset of nephritis. Kay[11] has shown that suppressing the production of these antibodies by roentgen radiation prevents the nephritis, whereas after radiation the injection of antibodies from another animal results in an immediate onset of nephritis. Thus it appears that the first antigen-antibody reaction is harmless, but when antibodies to foreign serum are present, a complex is formed that is nephrotoxic. The sequence of events in this type of nephrotoxic nephritis is similar to that in human nephritis, in which a latent period of three to twenty-eight days elapses following the initial infection before the acute episode is manifest, and is consistent with the concept of the causation of human nephritis advanced by Schwentker and Comploier[12] in 1939. In their view streptococcal products unite with the human kidney tissue to form a compound harmless in itself but causing antibody formation. The combination of the new antibodies and the original antibody-antigen complex is nephrotoxic.

Studies of the course of glomerulonephritis require many years of careful, tedious and arduous work to come to fruition because of the duration of the disease and the vagaries of its course. During the past year several reports have appeared dealing with the finding of various groups of workers in this field. Ellis[2-4] devoted his Croonian Lectures to a discussion of the natural history of Bright's disease, the result of twenty years' work. He states that glomerulonephritis appears in two forms, which he designates simply as "nephritis I" and "nephritis II." Nephritis I is the commoner of the two forms and appears predominantly in the first two decades of life. It is characterized by a sudden onset of the classic acute diffuse glomerulonephritis, usually following an upper respiratory infection. It proceeds in 82 per cent of cases to complete recovery, but in 10 per cent the disorder becomes latent with persistent proteinuria, terminating as a rule many years later in hypertension and renal insufficiency. Ellis is apparently of the opinion that the nephrotic syndrome is never seen in this group of patients, although it becomes the outstanding clinical manifestation in nephritis II. In this type of nephritis, a much smaller group, the onset is insidious, frequently without a history of a preceding infection, and occurs predominantly in persons in the second and third decades of life. Massive edema, hypoalbuminemia and albuminuria are the dominant and diagnostic features, and nearly all cases progress to a fatal termination in hypertension and uremia. Autopsy material is presented to support the claim that nephritis I and nephritis II are not only clinically unlike but are also definite pathologic entities.

Murphy and Peters[13] have reported a follow-up study of 205 cases of acute diffuse glomerulonephritis. Their findings are in agreement with those of the English workers in indicating a more serious prognosis in those patients who display edema after the first week or two of the disease. They emphasize that they find in their cases of acute nephritis a chronicity rate of at least 59 per cent, a figure in striking contrast to the much more favorable reports elsewhere in the literature. In neither their nor Ellis's study were the length and type of course subjected to further analysis, al-

though they agree on the variability and usual length. In this regard Horn, Klemperer and Steinberg[11] have made an interesting contribution, offering evidence to support the notion that the course of chronic diffuse glomerulonephritis may be divided into two phases, one slowly progressive and the other accelerated. This view is based on a clinicopathological study of 49 cases in which the anatomic equivalents of the changes seen in the benign and malignant phases of essential hypertension were found at autopsy. These changes were associated with histories of slow and of rapid progression, respectively. The authors believe that their data support the hypothesis that prolonged hypertension is the factor exciting acceleration.

There is a varying opinion regarding the prognosis of the initial acute phase of glomerulonephritis. In 495 cases brought together from seven reports, Hayman and Martin[15] found a range of 42.5 to 85.4 per cent cured, 17.3 to 32.0 per cent latent and 3.8 to 41.7 per cent going into chronicity. The greatest difficulty in prognosis is encountered during the latent phase into which many patients pass following the acute attack. This phase may be characterized by the complete absence of outright evidence of renal damage and is often mistakenly overlooked, or the patient is labeled as cured. Addis[16] was one of the first to emphasize the importance of this stage and to study it carefully with a technic of exacting urine examinations, including quantitation of the formed elements in the urine. Addis's method of counting the cells and casts in the urinary sediment continues to be a helpful adjunct in evaluating the progression and prognosis of the disease. Its superiority to the routine urinalysis is seen in the figures of Rubin, Rapoport and Waltz.[17] They found that the routine urinalysis returned to normal on the thirty-seventh day on the average, whereas a normal Addis count required an average of one hundred and twenty days. In addition, they found the sedimentation rate to be as reliable a prognostic index as the Addis count. Murphy and Peters[13] also recommended the sedimentation rate as a measure of the activity of the disease. From a practical standpoint, the technical simplicity of the sedimentation rate seems to recommend it as a valuable aid in following patients in the latent stage of glomerulonephritis.

There seems to be general agreement that rest is of first importance in the treatment of both the acute episode and the chronic form of glomerulonephritis. Murphy and Peters[13] state that the patient should be kept in bed until all clinical features and every evidence of nephritis have disappeared, or up to a period of four months. Of their patients, 27 per cent of those discharged with minimal activity became latent, whereas only 14.9 per cent of those discharged with negative urines went on to latency. However, many workers believe that there is no necessity limiting activity so long as hypertension and edema are absent. It is also agreed that dietary restrictions are indicated in the presence of azotemia and edema. In the former, protein should be limited, and in the latter, the restriction of salt and water is necessary. Whether protein should be cut down in the absence of azotemia remains a moot point. There is no clinical evidence that protein has any detrimental effect[18] and much evidence that protein lack can be harmful. On the other hand, protein feeding has been shown to increase the renal damage of experimental nephritis in animals.[19, 20] Most clinicians attempt to steer a middle course — the restriction of protein to minimal requirement levels.

The proof that localized infection and particularly infections of the upper respiratory passages and paranasal sinuses may give rise to glomerulonephritis has resulted in an earnest search for and eradication of focal infection. There is no evidence that these procedures ameliorate, interrupt or prevent the renal process. Illingsworth,[21] studying 119 children with chronic diffuse glomerulonephritis, could find no evidence that the course of the disease was altered by tonsillectomy. Nor could he demonstrate that tonsillectomy was of value in prophylaxis, since 20 per cent of a large series of patients had had tonsillectomy at some time before the onset of the acute nephritis. In another series, seen at the Babies' Hospital in New York City, approximately one third had had their tonsils out before onset.[22] Although it seems wise to remove tonsils and eliminate foci of infection in certain cases, this should not be done with the hope of affecting the nephritic process.

The effectiveness of chemotherapy in acute infections, particularly in those of streptococcal origin, has aroused the hope that the sulfonamides might prove effective in prophylaxis, in controlling and terminating the acute attack and in preventing exacerbations. This hope has been given some substance during the past year by the work of Williams, Longcope and Janeway.[23] These investigators treated a series of 42 cases of acute nephritis with sulfanilamide, using an untreated group of 108 comparable cases as controls. They concluded that foci of infection cleared up more rapidly, signs of renal damage disappeared more quickly, exacerbations occurred less frequently, the duration of the edema and the hypertension was shorter, and clinical recoveries were more frequent under sulfonamide therapy than in the

control group. Although their conclusions seem warranted by the data obtained, they were not able to present persuasive evidence on every point, mainly because of the irregularity of the course of the disease and the relatively small number of cases in their series.

Embolic and Other Forms of Glomerulonephritis

Whether the renal lesion appearing in the course of subacute bacterial endocarditis should be included among the nephritides is disputable, although it is widely classified as acute focal embolic glomerulonephritis.[24] Christian's[25, 26] work during the past year seems to support the idea that the lesion is inflammatory, at least in part. He was impressed by the nonspecificity of the glomerular lesions, which resembled those attributable to other glomerular damaging agents, such as acute diffuse glomerulonephritis, pyelonephritis and toxemia of pregnancy. In a series of 61 autopsies he found slight swelling and edema in almost all kidneys, hemorrhages varying from scattered petechiae to the typical "flea-bitten" kidney in 13 per cent and areas of infarction in 92 per cent. In 80 per cent the lesions were typical of those seen in intracapillary glomerulonephritis with diffuse proliferative intracapillary lesions, whereas in 16 per cent hyaline thickening of the capillary walls was observed. In addition, epithelial crescents were found in 36 per cent, with evidence of damage to the tubular tissue ranging from focal fibrous lesions in 26 per cent to complete disorganization in a few.

Other conditions in which acute diffuse glomerulonephritis is frequently seen are the visceral angiitides, including periarteritis nodosa, lupus erythematosus and Libman–Sacks disease. A study by Krupp[27] of the urinary findings in 21 cases of these disorders revealed an apparently specific picture in 14 consisting of the concurrence of red cells, red-cell casts, oval fat bodies, fatty casts, broad casts and heavy proteinuria. He believes this concurrence to be of diagnostic significance. The concept of Klemperer, Pollack and Baehr[28] that lupus erythematosus is a widespread disease of the collagenous connective tissue will undoubtedly inspire extensive investigation. This hypothesis is based entirely on pathological grounds and has as yet found no experimental proof. However, Rich's[29–31] belief that periarteritis nodosa is a manifestation of hypergy resulting from sensitization to foreign protein or drugs, such as the sulfonamides, appears to rest on firm experimental evidence. The discovery of extensive fresh lesions of periarteritis nodosa in 7 consecutive autopsies on persons dying in the midst of serum sickness or at the height of a sulfonamide reaction, as well as the experimental production of the lesions in rabbits during delayed reaction to foreign serums, gives strong support to his view. The finding of vascular lesions in rabbits following the production of antibodies to foreign serum has an important bearing on nephrotoxic nephritis, for the production of which these antibodies have been found necessary. Further exploration of the possibilities thus disclosed will undoubtedly add to the knowledge of the causation of many of the nephritides.

Pyelonephritis

Pyelonephritis has taken its place as a member of the group of Bright's diseases only during recent years, mainly as a result of the work of Longcope[32] and of Weiss and Parker.[33] The recognition that pyelonephritis can cause hypertension, with the terminal picture, clinically and pathologically, of chronic diffuse glomerulonephritis and malignant nephrosclerosis, and the realization that its initial lesion is amenable to modern therapy, has resulted in a voluminous literature. The acceptance of pyelonephritis with contracted kidney as a form of Bright's disease has not yet found its way into the textbooks, but in the current literature it is tacitly or explicitly regarded as such.[34] The fact that many cases of the affection are unrecognized in their incipiency raises the question of the relation of pyelonephritis to essential hypertension. The weight of the evidence, however, seems to support the belief that the disease is only slightly more frequent among hypertensive than among normotensive persons. Thus, Shure[35] in a review of 11,898 autopsies at the Cook County Hospital in Chicago discovered only 290 cases of pyelonephritis, with hypertension in 44.4 per cent as compared with 34.9 per cent in a control group. Among children, only 10 per cent of 79 cases were hypertensive.[36] Moreover, pyelonephritis seems to be a relatively rare disease (in Shure's series, 2.44 per cent of the autopsies), and since less than half of these were hypertensive, it does not seem likely that pyelonephritis is often an occult cause of essential hypertension. Harrison and Bailey[37] emphasize the importance and frequency of this condition as a complication of diabetes, since asymptomatic lesions leading to necrotizing pyelonephritis and death may occur in some 20 per cent of diabetic patients. Bowen and Kutzman[38] found an even higher percentage of involvement of the urinary tract in diabetic patients (51 of 84 cases), and they re-emphasized the difficulty of diagnosis. Actually the rarity of the lesion may be more apparent than real, since it may be unrecognized pathologically because of the terminal resemblance to chronic diffuse glomerulonephritis and nephrosclerosis. A higher incidence might

be found if the pathological criteria of Weiss and Parker[33] — an inflammatory reaction in the interstitium, colloid casts in the tubules, periglomerular fibrosis and evidence of infection or inflammation within the tubules — were kept in mind and applied.

An excellent review of the problems and literature of the glomerulonephritides by Matthews[39] has appeared during the past year.

The Nephroses

The group of disorders embraced by the nephroses are diverse in etiology and clinical manifestations, unified only by the fact that in all of them the tubular tissue contains lesions ranging from cloudy swelling with deposits of lipoid and hyaline material to profound necrosis. On the whole, they can be divided into two major categories: those in which the tubular lesions are as a rule of minor importance, with the nephrotic syndrome or proteinuria alone dominating the clinical picture, and those in which necrotic lesions of the tubules are outstanding, associated with few, if any, of the features of the nephrotic syndrome.

Among the entities included in the first group are lipoid nephrosis, amyloid disease of the kidney, intercapillary glomerulosclerosis, nephrosis due to deposit of Bence-Jones proteins in the tubules during myelomatosis — and as minor variants the so-called "larval nephroses" — and benign and orthostatic albuminuria. In all these the common denominator is proteinuria of varying degree. The pathogenesis of the proteinuria remains unknown and controversial, but it is widely held that glomerular capillary permeability is the determinant of the quantity of protein appearing in the urine. Dock[40] has advanced the thesis, on the basis of studies of the behavior of large protein-bound dye molecules, that a considerable amount of protein traverses the glomerular membrane normally and is reabsorbed by the tubules. In his view such entities as benign albuminuria, orthostatic albuminuria and other varieties of moderate protein loss may be attributable to tubular dysfunction rather than to increased permeability of the glomerular capillaries. Nonetheless, in cases of major proteinuria his concept must also embrace the notion of increased glomerular capillary permeability. Dock's hypothesis seems to gain support from the work of Smetana and Johnson.[41] These workers found that the colloidal and lipoidal droplets in the tubule cells of urodeles are derived from reabsorbed protein, a finding that indicates the possibility of protein reabsorption in the mammalian kidney and offers an explanation for some of the pathological findings in the nephrotic syndrome. An extensive study by Blackman, Goodwin and Buell[42] throws light on the components of lost protein and the significance of various types of proteinuria. In general it appears that albumin makes up the largest moiety of the protein lost, but in conditions of progressive renal failure associated with the appearance of fibrin and organized exudates within the kidney there is high globulinuria. Fatal cases of acute diffuse glomerulonephritis associated with high proteinuria and globulinuria showed extensive deposits of fibrin within Bowman's capsule, unlike fatal cases in which the proteinuria was of low concentration. However, the loss of protein in the urine, no matter what its mechanism, is the cause of the clinical picture in those conditions where proteinuria becomes excessive, for protein loss in excess of restoration causes hypoproteinemia, a lowered plasma oncotic pressure with subsequent edema, and the full-blown nephrotic syndrome.

The nephrotic syndrome is not limited to the nephroses, for it frequently appears in acute diffuse glomerulonephritis or in the course of chronic diffuse glomerulonephritis. It is interesting that this picture is always associated with an increase in the plasma lipids. The increase in blood lipid is regarded by some as a mechanism by which the lowered oncotic pressure may be compensated. However, Farr, Smadel and Holden[43] have shown that hyperlipemia is a constant feature of severe nephritis induced in rats by antikidney serum when there is no hypoproteinemia, and Heymann[44] reports that lipemia may occur on the basis of tubular damage in the absence of a decreased oncotic pressure. Heymann found a continuous rise in cholesterol and an even greater elevation in total fat following bilateral nephrectomy and fatal renal damage by mercury or uranium, but the levels returned to normal following hypertrophy of the remaining kidney after unilateral nephrectomy or healing of the renal damage. Winkler and his co-workers[45] also found an elevation in the phospholipids after bilateral nephrectomy and ligation of the ureters, but were unable to obtain increases after unilateral nephrectomy. They showed that the response was nonspecific, occurring in the monkey as well as in the dog, and was not due to fasting, dehydration or reduced plasma volume. An increase in the liver lipids indicated an extrahepatic source, and they expressed the opinion that the hyperlipemia might be due to a disturbance of a renal role in fat metabolism. In addition, Moschcowitz[46] found that hyperlipemia appeared in many conditions in which there was decreased metabolism, and he postulated that the hyperlipemia was caused by the decreased metabolism consequent on generalized edema. Thus there is no evidence that a disturbance of lipid metabolism is of primary im-

portance in lipoid nephrosis except as a phenomenon secondary to other changes.

Whether lipoid nephrosis is a distinct disease entity dominated clinically by the nephrotic syndrome, pathologically by lipoid deposits in the tubular cells and anamnestically by the absence of preceding renal disease, often with a fatal termination in the "nephrotic crisis" (explained below), is not certain. It is quite clear that the picture of lipoid nephrosis is extremely rare, for Schwarz, Kohn and Weiner[47] have seen but 40 cases in a twenty-year period at the Mount Sinai Hospital in New York City, where proportionately more cases are observed than elsewhere because of the intense and long-standing interest in the subject among many workers there. Of these 40 patients, 22 are now dead, of whom 12 were examined post mortem. At autopsy 5 showed definite glomerular changes. One case proved particularly interesting, for an onset of typical acute diffuse glomerulonephritis was followed by a typical clinical picture of lipoid nephrosis and death due to pneumococcal peritonitis. At autopsy only an occasional glomerulus with a thickened capsule and swelling of the tuft adjacent to it was found. The authors conclude that most children with the classic clinical picture have glomerular involvement, but perhaps in a different form than that seen in chronic or latent glomerulonephritis. Moschcowitz,[48] a member of the same group, concludes:

> The validity of "lipoid nephrosis" as a distinct disease entity depends on whether it possesses a precise background clinically and morphologically. Clinically "lipoid nephrosis" can be differentiated from conditions that simulate it only by arbitrary criteria. Anatomically, "lipoid nephrosis" has no specific or consistent background. . . . In the last analysis, "nephrosis" is not a disease and requires precise definition when the term is employed.

In any event, as Farr[49] has pointed out, the physiologic features and therapeutic implications remain unchanged regardless of the final position of the syndrome nosologically.

Considerable advances have been made during the past few years in knowledge of the physiopathologic phenomena associated with this syndrome. Farr[49] has recently written an admirable review of these advances, for many of which he and his colleagues are responsible. He is attracted to the idea that the syndrome is not essentially a renal affair. This notion finds support in the finding of a normal kidney function as measured by the urea and inulin clearances and in the evidence of a disturbance of protein metabolism. In both children and adults with the syndrome there is difficulty in maintaining nitrogen equilibrium even on high-protein diets. In addition, there appear to be abnormalities of the plasma proteins demonstrable immunologically and electrophoretically. Additional evidence that a defect in protein metabolism is responsible for nephrosis is found in the frequent occurrence of what Farr calls the "nephrotic crisis" associated with hypoaminoacidemia. The nephrotic crisis consists of an acute febrile episode with symptoms of peritonitis in the presence or absence of peritoneal infection. Farr and his associates have shown that these episodes are usually preceded by an accelerated loss of urinary nitrogen and a drop in the plasma level of the aminoacids. Intensive treatment with intravenously administered aminoacids or casein hydrolysates has not prevented or halted these episodes but seems definitely to have lessened the fatalities from them. In 32 cases treated with aminoacids, Emerson and Van Slyke[50] had no deaths, as contrasted with 66 per cent mortality when aminoacids were not used.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 29341

PRESENTATION OF CASE

A thirty-six-year-old white bank clerk entered the hospital because of increasing dyspnea of three months' duration.

The patient had had a long history of respiratory distress. Nineteen years prior to admission, while in college, he had had two attacks of pneumonia within a few months. Tuberculosis was suspected but chest plates failed to confirm the diagnosis. For the next ten or twelve years he was well except for more than the usual number of colds. Seven years before entry he was examined for life insurance; in view of his past history an x-ray film of the chest was taken which showed a lung tumor. He was admitted to an outside hospital where, following artificial pneumothorax, an exploratory thoracotomy was performed. A diagnosis of inoperable malignant tumor of the lung was made. He recovered from the operation and returned to work, free of symptoms.

During the next two years he lost about three months each year from his work because of upper respiratory infections. He was given x-ray treatment every three months. Two years later, that is, three years prior to admission, he had pneumonia again. About one year prior to admission he was told by his physician that they had considered his lung tumor malignant and incurable but that since he had lived for so many years they had become convinced that the tumor was benign. For the following two or three months he developed episodes of palpitation, which he believed were due to "nerves." These passed off and did not return. Three months prior to admission he had the grippe. Following this there was a gradual onset of dyspnea, which prevented him from walking up hill or climbing stairs. Three weeks before entry the dyspnea cleared up for a short time, but soon returned and became progressively worse. There was no history of tuberculosis.

Physical examination showed a thin, pale man with a sallow complexion. There was some increased prominence of the veins of the forehead and neck. The left border of cardiac dullness was 16 cm. to the left of the midline in the seventh interspace. The heart was otherwise normal. The lungs showed dullness over the right apex, becoming flat at about the level of the fourth rib. The entire right lower lung was flat, with absent breath sounds and decreased fremitus. The left lung was resonant, but there were occasional rales at the base. The abdomen was negative except for a tender liver edge, which could be percussed 8 cm. below the costal margin.

The blood pressure was 110 systolic, 90 diastolic. The pulse rate was between 100 and 130, and the respiration between 20 and 25. The temperature was normal.

The hemoglobin was 11.3 gm. per 100 cc., and the white-cell count 13,600. A blood Hinton test was negative. Two sputum examinations were negative for tubercle bacilli.

An x-ray film of the chest showed complete obscuring of the lower two thirds of the right lung field by fluid. The right upper lung showed increased density with honeycombing. A grid film showed the right main bronchus visible for about 2 cm., beyond which it could not be made out. The left lung field was clear. The heart shadow was tremendous, and the configuration suggested pericardial effusion (Fig. 1). Fluoroscopically no pulsation was demonstrable. The mediastinum was not displaced. Repeated x-ray examinations revealed no additional findings. A chest tap in the eighth space in the subscapular region yielded 30 cc. of light-amber fluid, followed by 220 cc. of what appeared to be whole blood. This was removed from several directions and depths. A repeat tap in the seventh space in the midaxilla again yielded 30 cc. of blood. No tumor cells were seen in the fluid, which contained innumerable red cells. Two days later the venous pressure was recorded at 330 mm. of water (normal control, 137 mm.). The patient was refluoroscoped at that time. A definite pulsation of the heart could be seen. No change in the contour of the heart could be demonstrated on changing the position of the patient from erect to horizontal. The left border of the heart shadow was convex and without any break in the smooth curve to indicate the limits of the pulmonary conus and left ventricle. Laminography showed the right main bronchus to end sharply 2 cm. from its bifurcation (Fig. 2). No air could be seen entering the lower and middle lobes. There was narrowing of the upper bronchus extending into the aerated portion of the lung. Several small air-filled areas were seen in the region of the lower lobe. A dense soft-tissue mass was seen lying between these and the

*On leave of absence.

blocked right main bronchus. The outline of the mass could not be clearly defined. An electrocardiogram was interpreted as showing sinus tachycardia, with a rate of 120, slight right-axis deviation, low T_1, total inversion of CF_2 and a very low T in CF_4 and CF_5.

The patient's dyspnea increased progressively. He died on the twelfth hospital day.

Differential Diagnosis

Dr. C. Sidney Burwell*: I should like to try to reconstruct some stages of this gentleman's course, beginning at the time he came into the hospital, to see what specific statements we can make that seem reasonably acceptable concerning the anatomic and functional situation of the heart and lungs.

In the first place it seems to me demonstrable that this man had an interference with the entry of blood into his heart — that he had pericardial tamponade. This conclusion is based on the following observations. He had distended neck veins and an elevated venous pressure; there is no mention of the development of collateral circulation from either the superior or inferior caval areas. We do not have a measurement of the venous pressure on the femoral vein, but there was evidence on physical examination that the liver was greatly enlarged and tender. I should accept that as evidence that he had an elevated pressure in his whole venous system. To that should be added the observation on his pulse pressure, which was very low, — only 20 mm., — with a low systolic and a high diastolic pressure. No statement is made about the presence or absence of paradoxical quality. The patient had an extremely rapid heart rate without fever, again a characteristic finding in those who suffer from obstruction of the entry of blood into the right side of the heart. This conviction of the presence of cardiac tamponade is strengthened by the observations that seem to indicate that he had a pericardial effusion of considerable size — namely, a very large heart shadow and what could be described as an "expressionless" heart, which neither moved nor exhibited the landmarks on the contour which we are accustomed to recognize. Thus he had a large, nonpulsating, smooth, heart shadow, combined with evidence of obstruction to the entry of blood into the heart, and I think we can say

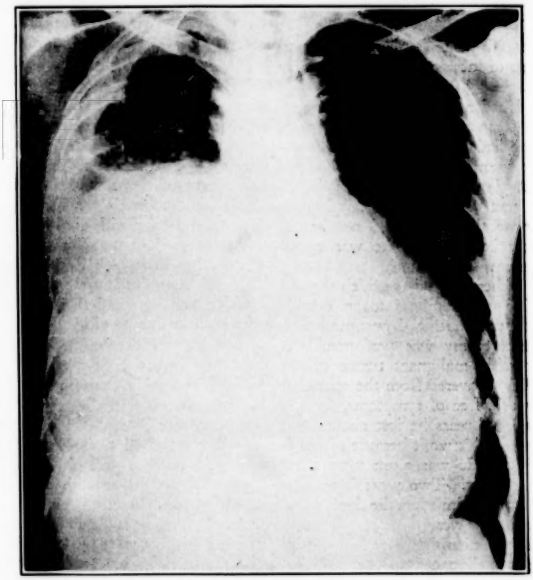

Figure 1. *Roentgenogram of the Chest.*

*Research professor of clinical medicine and dean, Harvard Medical School.

that he had pericardial effusion, with obstruction to the flow of blood from the venous system into the heart.

Now let us turn our attention to the pulmonary situation at the time he came into the hospital. That also seems to me to be impressive from the point of view of its mechanics rather than from the point of view of information concerning its etiology. The patient had, quite clearly, a long history of progressive obstruction to the bronchi series of collapses of the middle and right lower lobes, ending up in the situation in which he entered the hospital. More recently he had probably had beginning obstruction of the upper branch of the right main bronchus, with a similar change in the right upper lobe. Thus I should place pericardial effusion and pericardial tamponade as the first part of our diagnosis, and bronchial obstruction with atelectasis and bronchiectasis as the second.

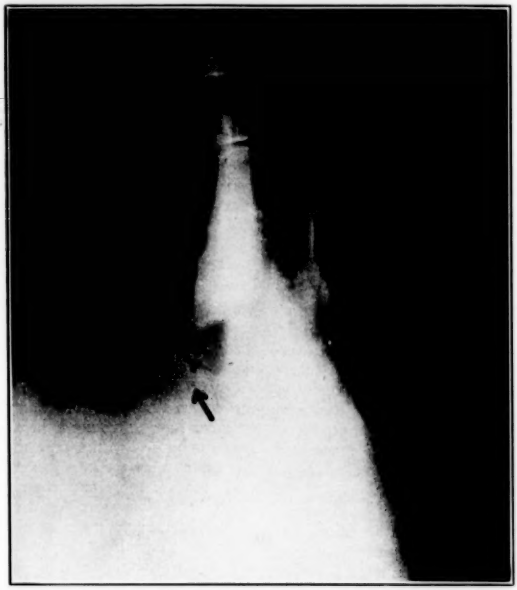

FIGURE 2. *Laminogram Showing Obstruction of the Right Main Bronchus Just below the Upper-Lobe Orifice.*

of the right lung. I surmise that the course of events was an obstruction to one or the other branch of the right bronchus, leading to atelectasis beyond the point of obstruction and to the development of bronchiectatic cavitation, probably recurrent infections in the atelectatic lung, destruction of lung tissue and the leaving of this honeycombed structure as the late result of bronchial obstruction. It seems to me that that meets the situation better than the possibility — the remote possibility it seems to me — of congenital polycystic disease of the lung. This man, I should say, had had a

Then we come to the most important and difficult part of the discussion — the basis for these mechanical changes in the lung and heart. Are they to be placed fundamentally on an inflammatory disease or on a neoplastic basis? Let us consider the possibility of a unitarian basis — that everything can be explained on one etiologic factor. What about tuberculosis? We know that tuberculosis of the bronchi is commoner than we thought; that enlarged lymph nodes in the mediastinum or the hilus of the lung may invade the bronchi and lead to inflammatory stricture and to

obstruction. Let us consider the possibility that he had reactivation of the mediastinal nodes and invasion of the pericardium by tuberculosis. It seems to me there are at least three very important pieces of evidence against the hypothesis that it had been or was tuberculosis, particularly the latter. One is the fact that he was quite free of fever, and I take it that the observation of a normal temperature was not a single isolated reading at a moment after a cold bath or something of that sort, but did really reflect the situation while he was in the hospital. I see from the chart that he never had fever over 101° F. and that it was usually around 99. That seems to me strong evidence, not final, against an active pericardial tuberculosis. The second piece of evidence against the possibility of tuberculous pericarditis is the presence of blood in the fluid that was removed presumably from the pleural cavity. It may have been removed from some other cavity in relation to the right lung, since the first tap conceivably might have been into the pericardium; but wherever it came from the fluid was so bloody that it was less characteristic of a tuberculous lesion than of a neoplasm involving either the pleura or the pericardium, or both. There is no particular case for the position, so far as I can find out, that a primarily tuberculous lesion may undergo malignant degeneration and be the site of tumor. Another important argument against the presence of tuberculosis is the observation seven years before entry, when his chest was opened and the surgeon, who had the inestimable advantage of a direct view, saw something he believed to be an inoperable malignant tumor of the lung. It is conceivable that that was on a tuberculous basis, but I think that it is much likelier to have been a neoplasm.

If we set aside tuberculosis, we are then confronted with the necessity of postulating a neoplasm. This is certainly the commonest cause of bronchial obstruction. Assuming it was a tumor, it had the extraordinary dual capacity of existing at least seven years — possibly more — and at the same time having done something recently that sounds very much like malignant invasion of neighboring structures. We must consider various types of benign tumors that obstruct the bronchus, — the adenomas and various other ones, — some of which may undergo malignant degeneration after years of growing. We must consider lymphoma. It does not appear in the record whether or not the x-ray treatment, which was faithfully administered, had any effect. However, if it had had an effect, we probably should have been so informed. I am trying to interpret that evidence, such as it is, as indicating that it was not the type of specific improvement after x-ray that we should expect if we were dealing with a lymphoma.

There is a curious silence about the state of this man's cough and sputum. I think one must interpret that as indicating that cough and sputum were not remarkable, and I derive from that the suggestion that hemoptysis was not a vigorously presenting symptom.

So we have quite an assignment — a neoplasm that obstructed the bronchus but did not produce much cough, did not produce large amounts of sputum, did not lead to hemoptysis and had lasted all these years, to explode in an extension to the pleural and pericardial cavities. At the time of the onset of his disease, this man was twenty-nine years old, a situation that further narrows the probabilities regarding the nature of the hypothetical neoplastic process. I do not think, by the way, that he had an aneurysm. There is no suggestion in his history or in the serologic findings. The patient was too youthful to have had an aneurysm that lasted as long as this, and I do not believe that the blood that came out at the time the chest tap was done was due to the entrance of the needle into an aneurysm.

If we ask ourselves what are the types of neoplasm that might fulfill this order, we certainly should have to consider carefully the small group of tumors arising from the mediastinum — the dermoid cyst, the teratoid tumor and so on. These do occur in men of this age. Most of them make themselves known before thirty or forty. Most of them have announced themselves, if they are going to grow, by the time the patient is forty. They almost always start in the anterior mediastinum and are more apt to go to the right than to the left. They are known to compress and occlude the right main bronchus or its main branches, and they may secondarily undergo late in their development the type of malignant change that it seems to me is suggested by the recent developments in this man's history. But, unhappily for me, he never spit up any hair or teeth or had any of the other charming observations that serve to make a positive identification of such a tumor. However, it seems to me that that group — probably a dermoid cyst with malignant change — fits the bill better than any other type of tumor I can think of.

The commonest tumor, of course, to give this kind of termination is bronchiogenic carcinoma. Bronchiogenic carcinoma with an onset at twenty is not impossible, but one that lasts for seven years is certainly an extreme rarity. According to what statistics I could put my fingers on, the great majority of people with bronchiogenic carcinoma do not live for more than five years. In fact the

longest duration that I could find in recorded cases of bronchiogenic carcinoma was between five and six years.

There is one other point. This man had had attacks of palpitation. Whether these were because he was nervous, or because he was anemic, or whether these attacks were associated with paroxysms of tachycardia or fibrillation I do not know. Such paroxysms occur frequently in people with pulmonary or mediastinal carcinoma, or with actual invasion of the pericardium by carcinoma, and the record does suggest that these attacks may have been brought on by such a mechanism.

I shall conclude by saying that I believe this man had a pericardial effusion, pleural effusion and bronchial obstruction with atelectasis, and that this was based on an extramural neoplasm that eventually involved the walls of the bronchi. This tumor was originally benign but eventually underwent malignant change and extended to the pericardium. Of all types of neoplasm, I consider a dermoid cyst to be the likeliest origin.

When one thinks of pericardial obstruction or distention in a case of neoplasm, one has to consider the possibility that it is due not to fluid but to actual invasion of the pericardial cavity by solid tumor. I know only two ways to make the diagnosis: to find cells in the pericardial fluid, which is comforting, or to see a shadow of the pericardium that is not smooth but lumpy. That may be inflammatory, of course, but is likely to be tumor.

Dr. Benjamin Castleman: Dr. Sweet, you said that the pericardium was tapped. Is that correct?

Dr. Richard H. Sweet: Yes. The reason it is not in the record is that I did it myself and forgot to write it down.

I did a pericardial tap through the paraxiphoid region first and obtained fluid readily. But it looked to me to be whole blood, and after drawing off a few hundred cubic centimeters, I withdrew the needle because I did not want to bleed the man to death. At the suggestion of Dr. Conger Williams, who saw this man with me, I then inserted the needle laterally to the first tap and the same kind of fluid was obtained; I could feel the pulsation of the heart muscle with the needle. We were sure that he had a massive effusion. Since the fluid was so much like whole blood and since the patient had a red-cell count of 2,500,000, I desisted. At a later chest tap we also removed whole blood.

Dr. Burwell: If it was fluid blood,—and I think it must have been,—that strengthens the case for rapidly growing neoplastic invasion. The presence of blood in the pericardium is due either to trauma, to cardiac rupture or to neoplasm. The inflammatory fluid from tuberculosis may contain red cells, but it is not usually grossly bloody.

What about his sputum?

Dr. Sweet: The patient never had any hemoptysis. He had a lot of cough and Dr. Burwell was correct in his interpretation of the bouts of what the doctors called variously grippe, pneumonia or what not, which must have been due to bronchial obstruction. After the patient died I obtained a report from the surgeon who operated on him seven years previously. He was convinced that the pulmonary tumor was a carcinoma.

Dr. Burwell: Not a shriveled-up lobe?

Dr. Sweet: No; he saw a large round mass.

Dr. Burwell: It was within the right lung?

Dr. Sweet: Yes, in the region of the middle lobe. Unfortunately no biopsy specimen was taken.

I never entertained any thought of operating on the patient, but tried to establish a diagnosis. My conclusion was that he had a teratoma.

Dr. Burwell: No teeth could be seen in any of the x-ray films?

Dr. Sweet: No; however, I do not mean a dermoid cyst. A teratoma behaves differently from most of the dermoid cysts in the mediastinum that I have seen.

Dr. Castleman: I am sorry that Dr. Conger Williams is not here, but I shall read his note:

> I am in favor of the diagnosis of pericardial effusion with tamponade to explain the findings of high venous pressure, paradoxical pulse and large cardiac shadow without evidence of valvular disease or anything to suggest diffuse myocardial involvement. Additional suggestive findings are left-border dullness 2 cm. outside the apparent apex impulse and narrowing of the border of superior cardiac dullness on the left in the sitting position in comparison with the lying position. There is probably some displacement of the heart shadow to the left, but it does not account for the large cardiac shadow. The blood pressure of 108/78 is not especially impressive, but does not exclude the diagnosis. The fact that the heart sounds come through well does not rule out pericardial effusion. Also in favor of pericardial effusion, as against heart failure, is the fact that the patient can lie flat on his right side without dyspnea.

Clinical Diagnoses

Teratoma of mediastinum, with extension to right bronchus and pericardium.
Pericardial effusion, with cardiac tamponade.

Dr. Burwell's Diagnoses

Malignant dermoid cyst of mediastinum, with extension to right bronchus and pericardium.
Pericardial effusion, with cardiac tamponade.
Pulmonary atelectasis and bronchiectasis.
Pleural effusion.

Anatomical Diagnoses

Carcinoma of the lung, with extension to pericardium, right auricle and pulmonary vein and partial obstruction to superior vena cava.
Pericarditis, acute and chronic, with hemorrhagic effusion.
Cardiac tamponade.
Pulmonary atelectasis, with cholesterosis, right middle lobe.
Hydrohemothorax, slight, right.
Pleuritis, chronic, fibrous, right.

ing bronchial obstruction. The middle and lower lobe bronchi were filled with tumor nodules. This tumor had extended medially to involve the right side of the pericardium, and the pericardial cavity contained a liter of bloody fluid. The visceral pericardium was covered with a shaggy brownish-red fibrinous exudate. The tumor apparently had extended through the wall of the parietal pericardium and had bled into the pericardial cavity. There was no actual tumor on the visceral layer, so that all this blood in the pericardial cavity was due to oozing from the tumor that

Figure 3. *Photomicrograph of Tumor Invading the Myocardium of the Right Auricle.*

Pathological Discussion

Dr. Castleman: There was only about 100 cc. of hemorrhagic fluid in the right pleural cavity, but most of the cavity was obliterated by dense fibrous adhesions. Most of the right lung was replaced by a grayish-white granular, soft tumor with many areas of necrosis, one of which formed a cavity measuring about 3 cm. in diameter in the lower lobe. The tumor involved the entire lower lobe and the lower four fifths of the upper lobe. The middle lobe was entirely collapsed and fibrotic and was mottled yellowish orange, owing to the large deposits of cholesterol. This so-called "cholesterosis" of the lung is not uncommon with long-standhad penetrated through the parietal layer. It had also penetrated through the right auricular wall into the auricle, obliterating a large part of its cavity, blocking the orifice of the superior vena cava, but without involving the endocardium. The tumor had also extended from the lung into the lower pulmonary vein for a distance of 4 cm. and had almost reached the left auricle. A photomicrograph (Fig. 3) taken through the right auricular wall shows tumor cells replacing the myocardial fibers. The tumor cells are epithelial in character. There is no stroma between the cells, and without knowing anything about the story I am sure every pathologist would call this straightforward carcinoma of the lung. With the infor-

mation that the tumor was of at least seven years' duration one might be justifiably skeptical of a diagnosis of carcinoma and might then bring up the diagnosis of endothelioma, possibly arising from the pleura.

DR. BURWELL: That would account for the extraordinary bleeding.

DR. CASTLEMAN: Most of the tumors of the pleura diagnosed as endothelioma are carcinomas of the lung with extension to the pleura. In fact we rarely if ever make the diagnosis of endothelioma. The cases that have been reported as endothelioma usually have nodules all over the pleura and are associated with a hemorrhagic effusion. There were no nodules on the pleura in this case. Another theory of the origin of this tumor is that it arose from a bronchial adenoma. The right bronchi were filled with tumor, which may have been benign years ago and then became malignant, as a few of them do. We know that adenomas are prone to extend through the bronchial wall and form large extrabronchial tumors. Perhaps the tumor felt seven years ago may have been an adenoma. If that were true, it is strange that the patient had no hemoptysis.

DR. BURWELL: That is what troubled me.

DR. CASTLEMAN: Nevertheless, I think we have to make a positive diagnosis at autopsy of carcinoma of the lung with extension into the pericardial cavity and into the heart. There was a metastasis to an intrapulmonary lymph node, close to the tumor, but no distant metastases.

DR. J. H. MEANS: Would you grade it as a slowly growing malignant tumor because it has been there for seven years? It must have been growing slowly.

DR. CASTLEMAN: It was not rapidly growing, but certainly not slowly growing.

DR. BURWELL: Is that not an extraordinary duration?

DR. MEANS: It does not seem possible that a carcinoma of the lung could have been present for seven years.

DR. CASTLEMAN: I was also puzzled and showed these slides to two other pathologists, who agreed to the diagnosis of carcinoma.

DR. BURWELL: Suppose it had been an adenoma. Might it not have developed deep enough in the mucosa so that it went outward instead of inward?

DR. CASTLEMAN: All the adenomas with extrabronchial extension that we have seen also have a nodule of tumor protruding into the lumen, unless, of course, it had been removed bronchoscopically.

DR. BURWELL: It seems to me evident that whatever this was seven years ago, it was a carcinoma at autopsy. The problem that has to be settled is the presence of an obstructing lesion seven years previously that eventuated into a carcinoma of the lung.

DR. CASTLEMAN: I believe that one can have a carcinoma of the lung of low-grade malignancy for seven years. A case that Dr. Allen discussed recently was a hepatoma of nine years' duration.* I think the whole idea of long-standing malignant tumors is something that we perhaps do not appreciate sufficiently.

DR. BURWELL: He had no hemoptysis.

DR. SWEET: No; which suggests that the tumor did not arise in a large bronchus.

DR. BURWELL: That is one of the reasons why I thought of an extramural source.

DR. SWEET: I was convinced all along, until I saw the autopsy, of mediastinal origin.

CASE 29342

PRESENTATION OF CASE

A twenty-nine-year-old housewife entered the hospital because of sharp pain in the right hip that radiated down the right leg.

Approximately five months prior to admission, without previous trauma, she developed sharp pain in the right hip that radiated down the right leg to the foot. At first this was mild and sporadic but during the previous four months the pain had occurred daily, had interfered with walking and had often kept her awake at night. On several occasions the right foot felt slightly numb and there were "pins and needles" in the foot. About three months prior to admission the pain became so constant and severe that she did not dare leave the house for fear that she would collapse. Five weeks before entry she fell down three stone steps, landing on her left side. After this her back was constantly sore.

Physical examination disclosed a thin woman who seemed comfortable. She walked with a slight tendency to favor the right leg. The pelvis was held level, but there were moderate lumbar lordosis and slight dorsal kyphosis, and the weight-bearing axis seemed displaced posteriorly. Examination of the heart and lungs was negative. In the right lower quadrant of the abdomen was a 1-by-2-cm. area of pigmentation suggestive of a "café-au-lait spot." There was no tenderness over the spinous processes. There was questionable fullness in the right lateral iliac fossa, and slight tenderness to deep palpation in the right pelvic fossa, but no mass was felt. There was no pain

*Case records of the Massachusetts General Hospital (Case 29331). *New Eng. J. Med.* 229:342-345, 1943.

on compression of the pelvic brims. Straight leg-raising on the right was limited to 75° because of tightness in the hip. However, there was a full range of hip and knee motion with the leg flexed.

The blood pressure was 95 systolic, 60 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood revealed a red-cell count of 4,280,000, with a hemoglobin of 80 per cent, and a white-cell count of 6300. The urine was negative except for a ++ Sulkowitch test for calcium. A blood Hinton test was negative. The serum calcium was 10.5 mg.; the phosphorus 3.0 mg., and the phosphatase 5.1 Bodansky units per 100 cc.

Stereoscopic x-rays films of the pelvis revealed a multilocular cystic defect with sharply defined borders extending from the crest of the right ilium to the acetabulum (Fig. 1). The bones involved showed slight enlargement. The cortex appeared normal. The remainder of the visible skeleton showed no evidence of decalcification. No abnormal soft-tissue masses were seen. The pelvis was slightly tilted to the left. Films of the right lower femur and of the upper part of the lower right leg showed no evidence of bone pathology. Films of the chest were negative. An intravenous pyelogram showed no evidence of renal pathology; the right ureter was slightly displaced medially in its lower portion, probably by the mass in the right ilium.

FIGURE 1. *Roentgenogram of the Right Ilium.*

An operation was performed on the twelfth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. FREDERIC W. RHINELANDER: We have a twenty-nine-year-old woman with a large multilocular cystic area in the ilium and pain of five

months' duration, which had become very severe at the end. Certain points in the history can be taken as probably being significant. The radiation of the pain down the leg is compatible with sciatica, which suggests a lesion in the region of the pelvis rather than one in the hip itself. The fact that the pain was worse at night is also suggestive of bone pain. The fact that the pain became so extremely severe is rather characteristic of tumor. The roentgen report states that the patient had a large lesion in the ilium. Thus, so far, everything in the history fits in.

She is said to have been a thin woman. There is no mention of weight loss, which, had it been a prominent feature, would probably have been put in the history. The displacement of the weight-bearing axis posteriorly is simply what one would expect with poor posture, and is not significant. The mass was palpable, probably deep in the left lower quadrant, which goes with the x-ray picture of something involving the right ilium. The "café-au-lait spot" was apparently a single pigmented area, which I shall discuss later. The fact that there was no pain on compression of the pelvic brim — that test is done to see if there is involvement of one of the joints of the pelvis — suggests that the lesion did not involve these joints. Straight leg-raising was somewhat limited, indicating tightness in the hamstrings, which goes with any lesion in this area that produces muscle spasm and has no diagnostic significance so far as we are concerned.

The blood picture is normal and does not help. A ++ Sulkowitch test is not significant unless the patient is on a low-calcium diet. This is not mentioned here, so probably that was not done. The Hinton test was negative, and the blood calcium and phosphorus were normal. The phosphatase was at the upper level of normal, or a little bit over by most standards; but with an extensive bone lesion, such as we see here, it would probably be considered normal.

May we see the x-ray films?

DR. MILFORD SCHULZ: This is the cystic lesion. It does not appear to expand the bone markedly and does not involve the hip joint. It is multilocular. There is no place where the cortex seems to be broken through. The edges are quite sharply defined. There is not much reaction of the bone at the periphery of the cystic lesion. I think that one would be quite safe in saying that it is a benign lesion. There are no other apparent lesions in the bone. As the record states, there is no decalcification, which tends to rule out a systemic disease that gives cystic changes in the bone. I do not know whether we can accept the displacement of the ureter as having anything to do with the lesion in the hip.

DR. WILLIAM B. BREED: Did I understand you to say that the ureter was displaced?

DR. SCHULZ: It is displaced medially at the brim of the pelvis.

DR. RHINELANDER: When these films are put in the stereoscope, one can see large cystic areas that, except for a little area at the wing, extend throughout the ilium.

Concerning the differential diagnosis, the most likely conditions are benign bone cyst, enchondroma, eosinophilic granuloma and giant-cell tumor. The others that should be mentioned are easy to rule out, and we can then come back to the more important ones. There is certainly no evidence of malignant disease. This is a large tumor, with a smooth surface and intact cortex. There is no evidence of infection in the clinical picture or the history. A gumma can occur in this area, but the Hinton test was negative and the x-ray films do not suggest it. Albright's disease[1] was probably thought of when the pigmented area was noted, but there is nothing in the picture to suggest that. The lesion was single and there is no mention of sexual precocity, which probably would have been brought out if that had been a serious consideration. Von Recklinghausen's disease of bone (generalized osteitis fibrosa cystica) is ruled out by the single lesion and by the normal blood calcium and phosphorus.

The age of the patient is against a benign bone cyst (localized osteitis fibrosa cystica). In this disease, most patients are under fifteen, and when it does occur in adults, it is usually a case of long standing that had not been discovered in early life, which is quite compatible with this story. Although pain is an uncommon symptom in benign bone cyst, in cases in which the lesion is so large, considerable pain may be expected. That is compatible with this patient's story of no pain in childhood. Pain may not be noticed in a deep-seated bone where there is not much function going on. The site is distinctly unusual for a benign bone cyst, which usually occurs in the shaft of one of the long bones.

The age of the patient is also against enchondroma, which is generally found in the phalanges; but that has to be considered. A multilocular cyst goes with either benign bone cyst or enchondroma.

Eosinophilic granuloma is distinctly uncommon in adults but it has been reported. The location, however, is rather characteristic. However, the large loculi and the integrity of the cortex in a tumor of obviously long duration are very much against this diagnosis, as they are against enchondroma.

The age goes with giant-cell tumor. The severity of pain is suggestive of this condition, but such a tumor occurs at the epiphyseal ends of the long bones, which rather effectively rules this out.

This is obviously an unusual condition. It does not fit in well with any of the lesions mentioned. It is in an unusual location. I think that it corresponds more with a benign bone cyst than with any of the other conditions. The large loculations that one can see in the stereoscope have the appearance of being empty; there is no evidence of cancellous structure, just the big loculi. The fact that the disease had been going on obviously for a great many years takes it back into the age group of benign bone cyst. It was probably present in childhood, when it was painless, and then reached a stage where it expanded the cortex somewhat. That is compatible with this condition, perhaps more so than with the others I have mentioned. Therefore I shall say that the most likely diagnosis is an extensive, localized, benign bone cyst.

DR. FULLER ALBRIGHT: I should like to vote for enchondroma. It looks much like another case that we have had recently.

CLINICAL DIAGNOSIS

Enchondroma or benign giant-cell tumor of ilium.

DR. RHINELANDER'S DIAGNOSIS

Benign bone cyst of ilium (osteitis fibrosa cystica localisata).

ANATOMICAL DIAGNOSIS

Fibrous dysplasia of ilium.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The lesion at operation was found to be cystic, and at biopsy, the wall of one of the cysts and the cortex showed dense fibrous tissue in which there were many bone spicules and areas of imperfectly calcified bone. The appearance is characteristic of what has been described by Lichtenstein and Jaffe[2] as fibrous dysplasia of bone. This is a condition that may affect one or several bones; it is usually unilateral and is believed to be a congenital maldevelopment of the bone-forming mesenchyme. Occasionally degeneration with cyst formation of this fibrous tissue occurs, and that is what probably happened in this case. It is the same condition that Albright[1] has called osteitis fibrosa disseminata, but is limited to one bone. I prefer the term fibrous dysplasia because it indicates both the pathologic anatomy and the etiology and because it lessens the confusion with von Recklinghausen's disease of bone (osteitis fibrosa cystica generalisata).

DR. ALBRIGHT: Then you would call it a bone cyst?

DR. CASTLEMAN: It all depends on what you mean by bone cyst. The term "bone cyst" usually applies to a single-chambered cavity occurring in the shaft of a long bone, close to the epiphysis. Other bone lesions, such as the osteitis fibrosa cystica associated with hyperparathyroidism, fibrous dysplasia and giant-cell tumor, may have cystic changes, but the fundamental condition is not a cyst.

DR. ERNEST M. DALAND: What is the prognosis and treatment?

DR. ALBRIGHT: Very good, I should say. The treatment is symptomatic. When it involves a long bone the treatment is that of giant-cell tumor. You curette out the tumor and fill it with bone chips.

DR. DALAND: There is a difference of opinion about filling with bone chips. We believe that it is unnecessary.

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"— OR ELSE"

The action implied by two words, "or else," uttered by Mr. Paul V. McNutt at the annual meeting of the American Medical Association in 1942 is apparently about to be taken by the Selective Service System to support the increasing demands of the War Manpower Commission. Married men with families who were engaged in nonessential industries have been inducted into military service, and it seems likely that the physician with dependents who has been declared "available" will be treated in a like manner. In fact, according to an editorial in the August 7 issue of the Journal of the American Medical Association, a directive has already gone to the commanding officers of the various service commands authorizing them, if necessary, to induct into service all such physicians between the ages of thirty-eight and forty-five.

The editorial goes on to state that the increasing tempo of the war effort necessitates an additional six thousand physicians in the armed forces by January 1, 1944. The need for these officers is acknowledged by the War Participation Committee of the American Medical Association and by the Procurement and Assignment Service. Indeed, it is so real that the status of physicians already declared "essential" will probably be reviewed to obtain from civilian life all those who can be spared.

The Journal has always asserted — possibly somewhat optimistically — that induction of physicians would never be necessary. If its faith in members of the medical profession is to be maintained, each physician who has been declared "available" and who has failed to offer his services must reappraise his position with a view to enlisting. If he waits for induction, it is likely that his eventual commission will be minimal, rather than according to his age and experience. Because of the need and because of the traditional patriotic response of physicians at such times, there still seem to be reasonable grounds for believing that "— or else" will be unnecessary.

THE DOCTOR PRESCRIBES A DIET

Just as the medical practitioner must be versatile, treating his patients for their real and apparent illnesses, advising them in misfortune and comforting them in affliction, procuring for them extra fuel oil in the winter and extra gasoline in the summer and prescribing for them additional allowances of rationed foods because of their varied appetites, idiosyncrasies and infirmities, so must he also be independent in thought and action, bold in diagnosis and original in treatment.

Nowhere can these latter virtues be more strikingly illustrated than in the prescription of diets, and never has the diet been a source of greater interest than in these days of apportioned food

supplies, of ration books and of red points and blue points. To the physician, as is his due, has been given the responsibility of prescribing foods for persons over and above the amounts allotted after careful studies of the available supplies with the knowledge that, when a limited amount is available, that which is given to one above his allotment must, in theory at least, be taken away from the rest.

The number of extra diets thus prescribed has been not inconsiderable; and although many of these requests can be granted out of hand by local rationing boards, when any question seems to exist concerning the propriety of a request, it is referred to the district branch of the Office of Price Administration. Here, if a doubt still lingers,—and, believe it or not, this office is discharging its difficult and thankless function of food rationing in a fair and intelligent manner,—the matter is referred to an advisory committee of physicians appointed for this purpose by the Council of the Massachusetts Medical Society.

During the last two months well over two hundred such requests have been reviewed by the Boston branch alone, and they illustrate beautifully the independence of thought and freedom from the bonds of tradition that the medical profession enjoys. For one patient, for instance, with duodenal ulcer, 40 pounds of processed foods per month, with no extra meats and fats, were prescribed; for another with the same disease, no extra processed foods, but 56 pounds of meats and fats were required. How true the old saying that one man's meat may be another man's poison! For a patient with gastric ulcer, 15 pounds of processed foods and no meats and fats were requested; for another, 48 pounds of processed foods and 83 of meats and fats for a month's allowance. A patient with hypertension and cerebral anemia apparently requires 180 pounds of processed foods and 55 of meats and fats for the lunar period, and one with partial hemiplegia, 143 pounds of meats and fats alone. Let us hope that the last stricken gourmand will have a butcher's assistance in carving his daily 4 pounds or so of porterhouse! A patient with gall-bladder disease, however, should receive the laurel wreath for his ability to assimilate 10 pounds per day, or 600 for a two-month period, of processed foods—practically enough to stock a small grocery store.

Processed foods—mainly fruit juices and canned, frozen and dried fruits and vegetables—actually present more of an economic and educational problem than they do a medical one. Meats, cheese and fats, most of which are rationed whether processed or not, are protective foods of greater vital importance. With a clear understanding of the value of such unrationed proteins as fish, poultry, milk and eggs, however, it becomes apparent that the generally accepted popular values placed on the red meats are largely esthetic ones.

A general discussion of diet and disease is beside the point. It should be emphasized, nevertheless, that if a reasonable degree of care is spent in apportioning ration points, few patients, regardless of their illnesses, require much in the way of food that their basic rations, together with the unrationed foods available, do not supply. For more detailed practical information the reader is referred to the article by Dr. Stare[1] and the letter of Dr. McLaughlin[2] in recent issues of the *Journal*.

Physicians, of course, will be besieged by seekers of special privileges. If such privileges are granted too liberally, however, and without particular knowledge of the circumstances, they will simply allow themselves to become the dupes of the unpatriotic, the self-indulgent and the unscrupulous.

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MEDICAL EPONYM

Bitot Spots

The true nature of these spots as indications of vitamin deficiency was unknown to their original describer, Pierre A. Bitot (b. 1822), professor of anatomy at the School of Medicine and honorary

surgeon of the Bordeaux hospitals, who published an article, entitled "Mémoire sur une lésion conjonctivale non encore décrite, coincidant avec l'héméralopie [Account of a Conjunctival Lesion not Previously Described, Coincident with Hemeralopia] in the *Gazette Hebdomadiere de médecine et de chirurgie* (**10**: 284–288, 1863), in which he reported 25 cases. A portion of the translation follows:

> The purpose of the present note is to point out . . . the coincidence of hemeralopia with a lesion of the conjunctiva; but this lesion does not involve the region of the pupils, forming rather on the eyeball, and consists not in an inflammation but in a collection of brilliant white points which produces what resembles a pearly or silvered spot at the side of the transparent cornea.
>
> This coincidence has neither been described nor even pointed out in the literature.

R. W. B.

RESOLUTIONS

RESOLUTION ON THE DEATH OF ROBERT TITUS PHILLIPS

The recently reported death in a Japanese prison camp in the Philippines of Major Robert T. Phillips, M.C., A.U.S., at the age of forty-one, came as a distinct shock to his many confreres and friends in New England.

To know "Bob" Phillips was to admire him and cultivate his friendship. Graduating from Tufts College Medical School in 1932 he served as house officer and resident on the Third Medical Service at the Boston City Hospital from July, 1932, to February, 1935, and was appointed junior visiting physician to the Boston City Hospital in December, 1936, resigning in August, 1938 when he left Boston to practice his chosen specialty in Portland.

From his college days he displayed unusual executive ability. When a student at Tufts he founded the William Harvey Society, an organization that has perpetuated his ideals and has provided for Tufts medical students, for more than a decade, lectures and seminars at regular intervals, given by national figures in medicine. He was secretary of the Tufts College Medical School Alumni for many years and was a stimulating influence in the reorganization and development of that body.

As a physician he was especially interested in arthritis and was a member of many medical societies. He was commissioned a lieutenant in the Medical Corps Reserve in December, 1932, and was called to active duty about six months before Pearl Harbor, being in the Philippines when war was declared. The last word from him was received by his wife on January 6, 1942, and told of the evacuation of Manila. Major Phillips wrote that he expected to go to Bataan, where he was taken prisoner. His parents, widow and four children survive him.

Be it resolved that the members of the Boston City Hospital hereby express their regret at the loss of a former beloved member of the Staff and extend to the members of his family their sincere sympathy.

WALTER T. GARFIELD, *Secretary*
Executive Committee
Boston City Hospital

RESOLUTION ON THE DEATH OF CHARLES MACFIE CAMPBELL

We, the Trustees of the Boston Psychopathic Hospital, hereby record our deepest appreciation of the fine leadership which Dr. Charles Macfie Campbell has given unfailingly for the good of our hospital service during the last twenty-three years. We have had a continuing opportunity to recognize and to value his admirable professional and personal qualities, and we have been proud of the many national distinctions which he has attained.

Our sense of loss, moreover, includes the poignant realization that a good comrade has passed from us.

We extend our heartfelt sympathy to the family of Dr. Campbell.

WILLIAM HEALY, *Chairman*
CARRIE I. FELCH, *Secretary*
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SPECIALISM

To the Editor: It has been called to my attention that, in an article entitled "The Universality of a Specialty," which was read before a student medical society in December, 1942, and published in the June 3 issue of the *Journal*, my statement that "the officer-of-the-day . . . though trained as an allergist or ophthalmologist must

nevertheless operate on any patient with an acute appendix who is admitted to the hospital at night during his tour of duty," is not in accordance with the present practice in the Army or Navy. I am informed that the officer-of-the-day acts in the same way that a surgical resident does. He sees all cases that are admitted to the hospital during his tour of duty and decides as to their disposition within the hospital. He can, if he wishes to do so, subject to the customs and orders peculiar to his own hospital and if such treatment is called for, operate on the case himself, call any other member of the staff in consultation or refer the case to any other member of the staff for operation by the latter officer. In the armed services, just as in civilian hospitals, the majority of residents exercise their prerogatives properly and with proper regard for the well-being and safety of the patients. That such proper regard is not always present in the armed forces any more than it is in civil life is evidenced by the illustrations cited above (which actually happened) and by many other similar instances of errors of commission or omission.

Despite the impropriety of my illustration, I see no reason to alter my conviction — as certain critics have suggested I should — that fundamentally the attitude of the medical department of the armed services is one which, as I stated, "still visualizes the general surgeon as a general specialist." This has to be and is properly so under combat conditions but should and need not be so in this country. In relation to neurosurgery in the Army it has been pointed out that sixteen hospitals have been designated by the Surgeon General as specialized hospitals for the treatment of such conditions. This does not mean that these hospitals receive only neurosurgical cases or that they are staffed exclusively by neurosurgeons. It does mean that somewhat more of the usual equipment and staff than exists in the ordinary general hospital has been made available for this specialty in these locations. Where large numbers of neurosurgical patients are concentrated and where the work is done under the direction of a man who has specialized in neurosurgery in civilian life, — as, for example, in the clinic at the Walter Reed Hospital, — no clinic in civil life can surpass and few can equal the calibre of care provided for such patients. There, the neurosurgeon does neurosurgery and nothing else. In other less active centers, however, this is not so. The neurosurgeon is expected to fill in as a general surgeon when there is nothing to do in his own department. Differences in technic, outlook and training in surgery as opposed to neurosurgery are disregarded. The patient whose abdomen would have been opened and closed in a half hour by the nonspecialist is endangered by the fact that the neurosurgeon, who is trained to a painstaking "puttering" type of operating, takes two hours to do the same thing. On the other hand, the general specialist who approaches a craniotomy in terms of a laparotomy will — as has occurred — lose his patient because of bleeding he has neither the patience nor the knowledge to stop or from postoperative surgical shock or circulatory collapse induced by his mistaken belief in the virtues of speed in operating.

A method of handling neurosurgical patients based on the assumption that a neurosurgeon should be able to act at will either as a competent general or as an equally competent specialized surgeon is, I submit, evidence of the conviction — not of junior officers of the medical departments but of those who make the governing policies of the departments — that general specialism as I have described it in my article is a good thing. Whether that is true or not is a matter of opinion that each reader will decide for himself.

DONALD MUNRO, M.D.

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BOOK REVIEWS

Lymph Node Metastases: Incidence and surgical treatment in neoplastic disease. By Grantley W. Taylor, M.D., and Ira T. Nathanson, M.D. With a foreword by Shields Warren, M.D. 8", cloth, 498 pp., with 61 illustrations and 117 tables. London: Oxford University Press, 1942. $8.00.

This is the first book of its kind to be published. The authors are to be commended for assembling a vast amount of information on the subject from the literature, for collecting data from three hospitals treating large numbers of cancer patients and for analyzing the results in such a way that proper conclusions can be made of the correct way to deal with metastasizing cancer.

The cases studied are from the Massachusetts General Hospital, the Collis P. Huntington Hospital and the Pondville Hospital (Massachusetts Department of Public Health). The authors are on the staffs of these hospitals and have participated in many of the operations on which they base their conclusions. During recent years, when this book has been in preparation, they have made detailed studies of the anatomic structures concerned in the dissections, the exact location of the nodes and the best types of incisions for each operation. Excellent drawings have been made of these dissections, and the reader may be assured that those shown are true representations of what was found and done at operation. The set-up of the book is pleasing and the subject matter is well arranged.

Part I deals with the anatomy of the lymphatic drainage areas. It is important to know the course of lymph drainage from various organs, the location of lymph nodes and the mechanism of lymph-node metastasis. Certain types of carcinoma are prone to spread along these channels. If the cancer is to be cured, the local process must be destroyed and the regional nodes must be removed. Again, if a metastatic node is palpated, a proper knowledge of lymph-node metastases allows the surgeon to search back for the primary focus. The various body regions have been studied for the exact location of lymph nodes. They are discussed in groups, such as the occipital nodes, the mastoid nodes and so forth, and their relation in the chain of nodes is brought out. Diagrammatic drawings of these lymph nodes in situ, the nodes numbered according to a key and the anatomic structures marked by legends on the side, are very effective. Lymph nodes of the head, neck, axilla, groin, pelvis, abdomen and thorax are demonstrated.

The regional surgical management of lymph-node metastases is the subject of Part II, in which 5481 cases of cancer are analyzed. In 48 per cent, lymph-node metastases were present. Careful study of these cases in groups is the basis for the conclusions and policies regarding treatment.

Lymph nodes may harbor metastases for some time before they become palpable. There is no close correlation between palpability of nodes and involvement by metastases, particularly when the nodes are small. When dealing with carcinomas of relatively low incidence of metastases, small palpable lymph nodes may be of no significance; however, with carcinomas known to metastasize early and widely, small nodes are of great significance. Nodes of more than a centimeter in diameter are quite likely to show metastases. If nodes are firm in consistence, metastases are likely to be present, although inflammatory or tuberculous nodes may be hard. Extension of the growth through the capsule of the node with resulting fixation usually indicates inoperability.

The time at which dissection is done influences the curability of node metastases. If block dissection can be done at the time of removal of the primary tumor, as in the breast, this is the preferable method. In some cases, such as those of the lip, dissection of the neck should be done as soon as the primary lesion has been treated and the wound healed. Dissection of nodes present for a long time or occurring some time after the removal of the primary lesion gives a much poorer prognosis than if early dissection is done. Prophylactic dissection may be advised even though no nodes are palpable, but the decision rests chiefly on the type of primary lesion.

The writers are skeptical of the value of prophylactic radiation of lymph nodes. They state, "It has not been demonstrated that such treatment prevents or diminishes or defers the occurrence of metastases." Preoperative radiation does, however, interfere with the healing of the operative wound. It is sometimes advocated on the basis of destroying cells spilled at operation; but if the case is properly selected and if adequate operation is carried out, there rarely is a recurrence in the operative field. If disease is left behind, radiation should be used; but if not, radiation should be reserved until recurrence takes place. Then sufficient treatment should be given to destroy the lesion.

Operations on lymph-node areas are described in Part III. Regional dissection of nodes is not advocated unless the primary lesion has been or can be cured. Fixation of nodes and widespread involvement are usually considered as contraindications to operation. The patient should be carefully prepared for surgery: deficiencies should be corrected and the operation should be done only when he is in the best possible condition. Block dissections should be carried out with great care. Sharp dissection should be used, with fine silk for ligatures. All serum and air should be expressed from the wounds, and pressure dressings should be applied. Most wounds are drained.

Supraomohyoid dissection is advocated for metastases from lesions of the lip and buccal mucosa and the skin of the central third of the face. The platysma muscle is always removed. The operative mortality among 601 patients in three hospitals was 1.5 per cent.

Radical neck dissection, with removal of all nodes down to the clavicle, the internal jugular vein and the sternomastoid muscle, as well as all tissues removed in the supraomohyoid dissection, is recommended for metastases from the tongue, floor of mouth and parotid gland. The mortality among 112 patients was 3.6 per cent.

Axillary dissections are done as part of the routine operation for carcinoma of the breast and for metastases from the arm or upper portion of the trunk. In breast operations, removal of the pectoral muscles is essential to gain access to the nodes of the upper axilla. When the lesion is on the extremity, transection of the pectoralis major is performed and the inner portion is left on the chest wall. The operative mortality among 1153 patients with carcinoma of the breast was 2.3 per cent, and that of patients undergoing axillary dissections for other lesions was nearly the same.

Inguinal dissections are advocated for malignant lesions of the lower extremities and for metastases from the anus, perineum and external genitals. Simple dissection is often sufficient if the primary lesion is on the extremity. Radical dissection, with removal of the fat and lymphatics along the external iliacs, is necessary for lesions on the anus or genitals. The operative mortality among 262 patients was 3.8 per cent. In nearly all the deaths, bilateral dissection was done in one sitting, and in several cases the primary lesion was excised at the same time. The authors advise that operations be done in three stages.

The entire book is well done and fills a very important place in cancer literature.

The Essentials of Emergency Treatment. 8°, cloth, 146 pp. New Haven, Conn.: *Connecticut State Medical Journal*, 1942.

The value of this little book to physicians who may be called on to do emergency practice should be great. If it were used by *all* chief medical officers in the Emergency Medical Service of the Office of Civilian Defense it would certainly be instrumental not only in reducing pain and infection but also in saving lives.

Throughout its chapters, surgical essentials are so clearly and simply presented that the volume is most readable, and the reviewer even ventures to add that it will provide an enjoyable evening's reading by the fireside with one's feet up and the favorite pipe functioning satisfactorily. This is no attempt at levity, but an emphasis of the way in which the material on complex subjects has been presented, without being weighted down by forbidding ultrascientific data.

It is difficult to pick out any one chapter as being better or more instructive than another — each chapter is in itself so worthwhile reading and digesting. The complexity of wound healing, shock and burns, for example, is presented simply and clearly. One does not have to be a professor of chemotherapy to understand it.

One statement, which now is erroneous, deserves comment. On page 56, in the chapter on burns, the author is discouraged at the lack of civilian plans for the storing of blood plasma. This section was written early in 1942, and at that time little had been done to provide adequate amounts of plasma for civilian use. Now, through the efforts of the Office of Civilian Defense and the United States Public Health Service, sufficient stores of plasma are available throughout the country for any civilian needs that might arise. Certain hospitals have been and are collecting, processing and storing plasma, and are distributing their surplus to other hospitals. The Office of Civilian Defense has also allocated many units of plasma to strategic communities.

The authors have done a great service to the medical profession in collaborating in this series of papers. The book should be on the desk — not on the shelf — of every practicing physician, and much of the factual material should be constantly kept in mind. The *Connecticut State Medical Journal* is to be highly commended for making this material so readily available to the profession.

Human Pathology. By Howard T. Karsner, M.D. Sixth edition. 4°, cloth, 817 pp., with 460 illustrations in black and white and 24 subjects in color on 16 plates. Philadelphia: J. B. Lippincott Company, 1942. $10.00.

The sixth edition of Karsner's textbook has appeared approximately at the same time as the seventh edition of W. G. MacCallum's textbook and the fifth edition of Sir Robert Muir's textbook.

In spite of the fact that Karsner's book is shorter than that of MacCallum and that it does not go so deeply into the details of descriptive pathology as does Muir's book, it is in many respects equal to either. It deserves to be recognized as one of the three standard works in pathology of our time. Its especially valuable feature is the bibliography at the end of each chapter. There is evidence of profound knowledge and excellent choice, valuable not only for the beginner but for the mature pathologist. In many respects Karsner's book is a bonanza, demonstrating the wide experience, the close observation and the sound judgment of the author. Two good examples of this are the discussion covering the persistence of cartilage discs between the vertebras in cases of pulsating and excavating aneurysms of the aorta and that regarding the reactivation of latent syphilis by the intercurrence of acute infections.

But it is the duty of a reviewer to find some grounds for adverse criticism. It would seem better to consider infectious monocytosis in the chapter on infectious diseases than with the diseases of the reticuloendothelial system. If the heterophile antibodies are mentioned, their interference with the Wassermann reaction by giving a nonspecific positive should be mentioned. Although undulant fever is one of the diseases rarely seen by the pathologist at autopsy and although but few references to autopsy findings are found in the literature, it deserves mention in a textbook of pathology. In the chapter on glanders, since testicular foci are practically pathognomonic, they should be mentioned, especially because the edema of the seminal cord in infected animals is cited by the author. Agenesis of the kidneys is not limited to monsters.

In general, it may be said, that the sixth edition deserves to acquire new friends among students and doctors. For coming editions one might suggest a more elaborate description of certain aspects of pathology, for example, the biologic and structural peculiarities of infancy and old age.

The Dynamic State of Body Constituents. By Rudolf Schoenheimer, M.D. 8°, cloth, 78 pp., with 16 tables. Cambridge: Harvard University Press, 1942. $1.75.

In considering reactions taking place within the living body, many substances long held to be relatively stable have been shown of late to be subject to reversible equilibria. Schoenheimer has characterized this situation as "a steady state of rapid flux."

Much of the experimental work leading to this radically new concept has made use of isotopically labeled compounds. Schoenheimer, a leading experimenter with the stable isotopes, summarized the most critical of his experiments and the sequential physiologic conclusions for the Dunham Lectures of October, 1941. The majority of the experiments utilize food stuffs (fats or amino acids) or metabolic intermediates (arginine or creatine) marked with introduced isotopes of hydrogen or nitrogen. Some few of the studies are startling in their simplicity. Fasting rats were, for example, injected with heavy water, and deuterium was found in all the amino acid fractions, except lysine, isolated from the animal's proteins twenty-four hours after the injection. For the details of the more complicated studies the original book should be consulted. The activity of glutamic acid in reversible dehydrogenations and in transaminations is repeatedly emphasized.

Death intervened before the lectures were delivered; Dr. Schoenheimer's colleagues completed the necessary revisions. Dr. Hans T. Clarke presented the lectures, which appear in this small volume.

Psychiatry in Medical Education. By Franklin G. Ebaugh, M.D., and Charles A. Rymer, M.D. 8°, cloth, 643 pp., with 16 tables and 7 charts. New York: The Commonwealth Fund, 1942. $3.50.

The authors have made a complete survey of the teaching of psychiatry in medical schools in this country, both to undergraduates and postgraduates. They have also examined the teaching facilities in general as well as special hospitals. The various methods of teaching are analyzed. A marked variation in methods of instruction in colleges and hospitals was found; no uniform agreement in regard to how psychiatry ought to be taught exists. Some schools give reasonably satisfactory courses, but in many the instruction is poor and inferior. Since psychiatric teaching is in a confused and unsatisfactory state, the needs for this survey are clearly indicated. Emphasis is rightfully put on the value of personality studies and the treatment of the whole patient — a total person with a mind as well as a body.

For the teacher of psychiatry, there is important material in the appendices to this book. The "personality study" used at the Johns Hopkins University School of Medicine and elsewhere is given in full. An outline of lectures in psychiatry and a list of central agencies for the direction of state institutions will also be found useful.

The book, in general, is adequate in every respect. From its use should come important advances in the teaching of psychiatry in the United States and elsewhere.

Ovarian Tumors. By Samuel H. Geist, M.D. 8°, cloth, 527 pp., with 312 illustrations. New York: Paul B. Hoeber, Incorporated, 1942. $10.50.

This monograph is a thorough résumé of knowledge of ovarian tumors up to 1936. The embryology, anatomy and physiology are considered in some detail. There follows a discussion of each group of ovarian tumors represented in the classifications of Pfannenstiel, Sternberg, Goodall and Meyer. The references, which are many, include practically all the foreign articles on the subject but few references to American reports or investigations.

The book lacks an adequate discussion of the laboratory findings in cases of endocrine tumors of the ovaries, such as, reports of 17-ketosteroid and follicle-stimulating-hormone determinations, reports of the amount of estrin in the fluid of follicle cysts and so forth. There is some discussion of the problem, however, in the section on granulosal-cell tumors of the ovary.

This book is a satisfactory review of Dr. Geist's vast experience and of the foreign literature and, as such, is a valuable addition to knowledge of the ovarian neoplasms.